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INDIVIDUAL CONSTITUTION AND ENDOCRINE GLANDS*

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Experience has long taught us that important branches of science in the beginning of their development are likely to be overestimated. In the history of medicine there are numerous examples of this psychological phenomenon. Cellular pathology as well as bacteriology and, lately, also endocrinology are prominent instances. Wherever unexplainable facts or conditions occur, attempts are usually made to clear them up by means of the newly developing science, taking mere hypotheses for established facts. In such a period of marked confusion of ideas it seems permissible to exercise a certain amount of criticism and, where possible, actually to revise and to correct certain existing opinions. Especially with regard to endocrinology it would appear useful to point out in our discussion some new or at least insufficiently emphasized views.

It is a well known fact that the general habitus of young male individuals undergoes characteristic changes when they

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The cited literature is to be found in J. Bauer, Konstitutionelle Disposition in inneren Krankheiten. J. Springer, Berlin, 3 edit. 1924, and J. Bauer, Vorlesungen uber allgemeine Konstitutions und Vererbungslehre. J. Springer, Berlin, 2 edit. 1923.

are deprived of the influence of the endocrine part of the genital glands. Whether they have been castrated at an early age, or have lost their testicles by an inflammatory or

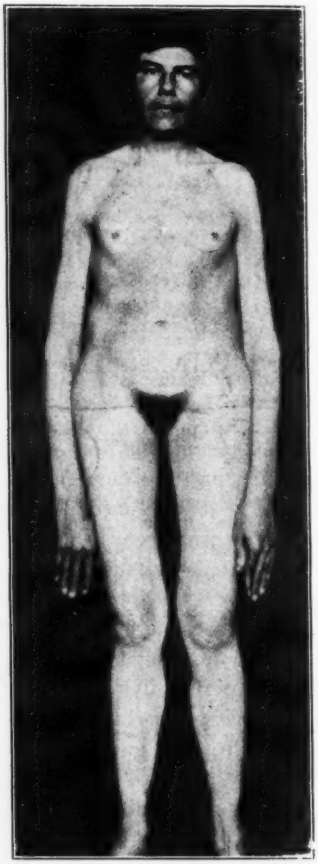

Fig. 1. Eunuchoid tallness (after Tandler and Gross).

neoplastic process, by an injury or through hypoplasia of the genital glands from birth, entirely regardless of the cause, the same change in the general make-up is observed. Generally speaking this change in the habitus of the young male without

the functioning endocrine component of his testicles manifests itself in what is usualy accepted under the name of eunuchoidism.

According to Tandler and Gross, two varieties of such eu-

Fig. 2. Eunuchoid stoutness (after Tandler and Gross).

nuchoids may be differentiated: first, eunuchoid tallness or gigantism, and, secondly, eunuchoid stoutness or obesity.

In the first case (Fig. 1) we find that the tallness is due to disproportionate length of the extremities, as is evidenced by

measuring the length from the top of the head to the superior border of the pubic bone and comparing it with the length taken from the superior border of the pubic bone to the sole of the foot. The former measurement is spoken of as the "superior length," and it surpasses considerably the latter, which is spoken of as the "inferior length." In normal adults these two distances are approximately equal and the entire length of the body corresponds nearly perfectly to the reach of the outstretched arms. In pure cases of eunuchoid tallness, we find the reach of the outstretched arms to be usually greater than the body length in consequence of the extreme length of the extremities

In pure cases of eunuchoid obesity (Fig. 2) the localization and distribution of the subcutaneous fatty tissue is the characteristic feature. Accumulation of fat around the hips, in the lower abdominal region especially above the genital organs, in the buttocks, breasts and thighs, resembling closely the fat distribution of normal females, characterizes this type of eunuchoidism. Border line cases between these two groups are not infrequent.

The fact that the same primary defect of the male genital organs may be followed by two different types of abnormal development and growth shows that the results of insufficient secretion of the genital hormone are determined not only by this fact alone but also by something else situated in the rest of the body, namely, by the special kind of reaction of the organism to the genital insufficiency. It is generally assumed that the quality and reactivity of all the rest of the endocrine apparatus may explain the different results of a primary hypogenitalism. Individuals with a rather well developed and functionating hypophysis, with a certain constitutional tendency to pituitary, and perhaps also to thyroid hyperactivity, would become eunuchoid giants; individuals with a less developed and active hypophysis, with a slightly exhausted pituitary and perhaps also thyroid function, would show the characteristic signs of eunuchoid stoutness.

This explanation seems at first sight quite evident, but it is decidedly unsatisfactory when we consider a number of obvious facts. First, we could not explain the border line cases mentioned above, where characteristic features of eunuchoid tallness with eunuchoid obesity are combined, for we cannot assume a

hyper- and a hypo-activity of the pituitary gland at the same time.

A second fact would seem to be particularly interesting. The eunuchoid skeletal proportions are usually explained according to Tandler and Gross by the abnormal persistence of non-ossification of the epiphyseal junctions in the long bones of hypo-

Fig. 3. Eunuchoid proportions in a 12-year-old girl (after Strats).

genital persons. When the ossification of these junctions is delayed, the longitudinal growth may persist for a longer period and the natural consequence would be the overgrowth of the extremities, that is to say eunuchoid proportions of the body,

provided a sufficient activity of the pituitary and thyroid glands is present in order to stimulate the growth in general.

This theory however cannot satisfy any longer since, as I have pointed out, eunuchoid skeletal proportions are sometimes to be found even in dwarfs, especially in hypopituitary dwarfs, as well as in children whose epiphyseal junctions are not yet ossified at this period of life. (Fig. 3.) Disproportionate length of the extremities can therefore not be explained solely by a longer duration of longitudinal growth on account of delayed ossification of the epiphyses; that it can exist also when there is an insufficient function of the pituitary gland is quite obvious. There must still be something besides the endocrine glands which governs proportionate growth and which may be responsible for eunuchoid proportions of the body under certain conditions. We are forced to assume that the cells of the osseous system and especially the cells forming the epiphyseal part of it must have their own power of proliferation and of growth, although they may be influenced by certain hormones. Were we able to eliminate the endocrine glands we would be obliged to acknowledge a certain autochthonous automatism of the bony tissue itself. The endocrine organs influence the growth, but they alone do not bring it about; without them we would observe a certain amount of growth too. Normal growth is the product of co-operation of autochthonous growth of the skeleton cells with certain endocrine glands stimulating or checking it. The autochthonous power of growth, however, is to a high degree a constitutional characteristic of the individual, it is transmissible by inheritance and must therefore be potentially localized somewhere in the germ cells. Otherwise we could not explain, for instance, the great racial and family differences of growth and body length; but especially we could not explain the marked eunuchoid proportions of some negro races that show no signs of hypogenitalism, but on the contrary, possess larger genital organs than are usual in white races and reach puberty generally much earlier than the latter.

We may sum up the facts as follows: eunuchoid proportions of the body cannot be explained merely by delayed ossification of the epiphyseal junctions of the long bones and hyperactivity of pituitary or thyroid; the constitutional autochthonous tendency of growth of the bone cells themselves must be considered

as an important, individually different, factor determining not only the definite body length but also the body proportions. There must exist, however, a certain relation between the insufficient or absent endocrine genital function on the one hand and the increased tendency to longitudinal growth of the extremities on the other. It is very probable that the genital hormone checks directly this longitudinal growth, but the results of the insufficient or absent genital hormone are not only dependent on the absence of this checking influence, but primarily on the constitutional growth-power of the bone cells themselves. When this constitutional growth-power is very high, then eunuchoid proportions may be observed also without a genital insufficiency, notably in negroes (as a racial characteristic) and in certain children; when it is moderately high, but not extreme, then the absence of the checking genital hormone alone may produce the characteristic eunuchoid proportions; when it is only slight, then not even the lack of this checking influence will be sufficient to increase the length of the extremities. The loss of the specific genito-hormonal inhibitory influence upon the longitudinal growth of the extremities can become manifest also in pituitary dwarfs in whom the general growth of the body is diminished by the absence of a hormonal stimulus. It can be paralyzed, however, by the lessened autochthonous growth in cases of general under-development, or general growth insufficiency, and in cases of so-called universal infantilism, where a certain degree of hypogenitalism is only a part of the general hypoplasia, just as the small genital organs of a child correspond to the size and development of the whole body. Just as a child usually does not show eunuchoid skeletal proportions, so they are absent in cases of universal infantilism.

A thorough analysis of a quite different state of constitutional growth disturbance, of the so-called chondrodystrophia or achondroplasia, and of its rudimentary type, chondrohypoplasia (Fig. 4), reveals another connection between the longitudinal growth of the extremities and the development and functional activity of the genital organs. Chondrodystrophic dwarfism is characterized, as is well known, by more or less extreme shortness of the extremities entirely out of proportion to the trunk

and head. Those dwarfs often show marked signs of hypergenitalism. Their external genital apparatus is disproportionately large, puberty is reached early, and the activity of their sexual organs is sometimes extremely high. The secondary sex characters are usually very well developed and several authors have sought also the explanation of the strong development of the musculature, the high intelligence, and the peculiar hypomaniac mental state in a primary hypergenitalism. It is well known that achondroplastic dwarfs were especially used as court jesters and are at premium as clowns. Therefore, a great number of authors (among them Poncet and Leriche, Lauze, Bertolotti, Parhon, Rebattu, G. A. Wagner) have suggested primary hypergenitalism as the cause of this growth anomaly. This suggestion, however, is unacceptable.

The shortness of the extremities in achondroplasia cannot be due to a hyper-production of the genital hormone checking especially the longitudinal growth of the extremities, since this shortness is to be found even in new born children. It is certainly due to a constitutional anomaly of the skeletal cells themselves, to a hypoplastic state of the cells at the epiphyseal junctions determining the longitudinal growth by their activity. Anatomical researches, especially those of Kaufmann, have demonstrated the abnormal state of these cells; sometimes they are markedly hypoplastic, sometimes altered in a more severe way—irregular, or showing a mucoid degeneration. This severe type of the so-called malacic chondrodystrophia is to be observed only in new born children, since such individuals are usually not able to remain alive. Cartilaginous exostoses near the epiphyseal borders, often found in achondroplastic dwarfs, demonstrate also the primary abnormal state of the bone tissue in certain parts. Of particular importance, however, are the rare cases of hemilateral achondroplasia, or partial achondroplasia, where only one side or only one extremity is affected by this anomaly. (Fig. 5.) It is quite impossible to explain these peculiar conditions by a hormonic influence that must manifest itself in the whole body and could never bring about such a partial deficiency.

Neither the increased check of the longitudinal growth by the genital hormone nor a premature closure, that is ossification

of the epiphyseal junctions, can therefore be the cause of the disproportionate shortness of the extremities in achondroplastic dwarfs. Regarding the last point it may be mentioned that Japanese commonly cease to grow long before the appearance of puberty, just the contrary of what we have stated before of some negro races. And yet a certain relation between insufficient longitudinal growth of the extremities and hypergenitalism is not to be denied. The cause of the hypoplastic state, of the

Fig. 4. Chondrohypoplasia.

Fig. 5. Partial achondroplasia

insufficient activity of the cartilaginous cells in the epiphyses of a chrondrodystrophia, is an abnormal constitution of these cells due to an abnormal state of the germ cells as chondrodystrophia is a typical hereditary pathological condition.

According to the well known doctrine of modern heredity, which we owe primarily to the admirable investigations of Morgan and his associates, we must assume that in a certain part of

the chromosomal apparatus of the fertilized ovum there exists somewhere an alteration, an abnormality, which represents the abnormal state of the special skeletal cells in the fully developed individual. To the constitutionally and hereditarily abnormal state of this part of the body and particularly of the skeleton there must correspond an abnormal state somewhere in the chromosomal apparatus (with its probable 12 chromosomes) in the mature human germ cells. It seems necessary to recall that these 12 chromosomes represent very probably the totality of transmissible qualities that are to be imagined as localized in some way in these little bodies. It is impossible and surpasses the limits of natural science to attempt a more detailed explanation of this fact. But what is settled as a matter of fact in the general science of heredity is to be applied also to the human organism. Further, we have to remember that during the evolution of the whole organism from a single fertilized ovum, a part of every one of these chromosomes later enters every new body cell. The marvellous mitotic cell division provides for the equal distribution of the chromosomal material to every one of the new cells. Every cell of our body possesses, therefore, the same chromosomal material as the fertilized ovum from which our body originated. But this chromosomal material represents at the same time the potential power of specific differentiation of the cells, providing innumerable new cells and forming in this way the different parts of our body. The specific structure of the chromosomes with their potential power to bring about quite a specific differentiation of the cells and cell complexes is responsible for the characterization of the species, race, family, sex and a great many of the individual peculiarities which are potentially determined and fixed at the moment of fertilization. Every cell of the body gets the same amount of chromosomal material by the mitotic cell division, but the potential power to bring about quite a definite differentiation of the cells with quite definite and specific characteristics—this potential power has become effective during the developmental process and has been used up to a different degree, depending upon the different final state of the cells. We call the great number of different latent characteristics (localized somewhere in the chromosomes) unit-

characters or Mendelian units, as they are transmitted to the descendants according to the rules of Gregor Mendel.

But what we assume to be the material substratum of those units must be present, therefore, in every body cell. The units responsible for the development of a particular body length, of a particularly long nose, of musical endowment, or of red hair will be present in every cell of the body, but they will be efficacious in a quite different way in the different cells. The units for body length will manifest themselves in the cells of epiphyseal cartilages, the units for a long nose in the cells forming later the constituents of the nose, the units for musical talents in certain brain cells and the units for red hair in the cells producing the hair pigment. In the remaining cells of the body all these different units stay inactive and latent, only in the germ cells they keep their whole latent power undiminished, in order to manifest it when the germ cell happens to meet with a second germ cell of the other sex. We may speak of units as chromosomal potencies, which are present in every cell but which become active only in a few special cell-groups, according to the kind of these units. In lower organisms where the power of regeneration is higher or even complete, the presence of all units in every cell is quite obvious. The chromosomal potency representing the Mendelian units is the highest known, almost incomprehensible, store of potential energy.

After this digression from our subject we may return prepared to apply to it the statements of the general science of heredity. In a certain part of the chromosomal apparatus there must be localized the constitutional tendency and power of the epiphyseal cartilaginous cells of the long extremity-bones to proliferate, to grow, and to bring about a certain proportionate length of the limbs. In the pathological condition of achondroplasia this tendency and power is diminished. But according to our former statements bearing upon the relation between achondroplasia and hypergenitalism and corresponding to the experiences and interpretations of the general science of heredity we must assume that these two constitutional anomalies are very often associated with each other, because their chromosomal localizations lie close together and, therefore, either both are often affected with an anomaly at the same time, or the cor-

responding units have a certain influence not only upon one but also upon the other of the two characters. One uses for this phenomenon the term pleiotropic units. We speak of this as a *germinative or chromosomal correlation* and must suppose that such a correlation exists between the unit governing the longitudinal growth of extremities and the unit governing the development of the genital apparatus.

An entirely analogous chromosomal correlation is to be observed, for instance, between a constitutional fragility of the bones (the so-called osteopsathyrosis idiopathica) and a thin blue sclera, or, according to my own investigations, between red hair and freckles. The tendency to become freckled, particularly at places that are usually not exposed to sunlight as the nape of the neck or forearms, is certainly correlated with the tendency to red hair pigment in the chromosomal apparatus, because we find not only the combination of red hair with freckles in the same person, but often separated from each other in different individuals of the same family. A patient of mine with dark and partially gray hair but with numerous freckles at the nape of his neck was rather surprised when I asked him who in his family had red hair. His sister had, as a matter of fact, fox-red hair!

In our case of correlation between the chromosomal potency for longitudinal growth and that for genital development, this germinative chromosomal correlation is associated with a real hormonal correlation, as we pointed out before with regard to the checking influence of genital hormone upon the longitudinal growth. This peculiar kind of double correlation, germinative and hormonal, is to be observed also in other instances, particularly the correlation of the development of the genital glands and that of the so-called secondary or accessory sex characters.

According to the most interesting facts revealed by experimental and clinical endocrinology the consideration is usually ignored that this correlation cannot be a pure hormonal one, but that the genital hormones have only a stimulating, increasing, or as Halban called it twenty years ago, a protective influence upon the development of the secondary sex characters. But those characters are established and fixed potentially at the same moment as the sex of the genital glands and the genital organs; they are correlated with them in the germ; there exists not only

a hormonal but also a chromosomal correlation between them. The striking fact, that the so-called secondary sex characters can be influenced and under certain conditions even abolished by removal of the genital glands, that by implantation of heterosexual genital glands on castrated guinea-pigs even some heterosexual characters may be provoked (Steinach)—these facts well known and easily to be understood as a consequence of hormonal correlation hide to a certain degree a number of facts pointing towards a germinative correlation between genital glands and secondary sex characters.

According to the well established studies of the science of heredity, sex is determined at the moment of fertilization of the ovum by a certain constitution of chromosomes. But determination of sex does not mean merely testicles or ovaries, but to a certain degree also, all other characteristics of the body and soul that are different in the two sexes. Long before puberty we recognize the typical male or female temperament. Boys are more frolicsome and noisy; girls are neat and vain; boys play at soldiering or fighting; girls prefer dolls and taking care of smaller children. Experienced pediatricians are able to recognize boys or girls in new born children solely through a somewhat different shape of the face and head. If one object that testicles and ovaries have to fulfill their endocrine functions long before puberty and even during intrauterine life, then I should ask him why a large number of secondary sex characters, such as voice, hair-growth, fat distribution, libido and so forth, do not develop before puberty associated with a marked growth of the genital glands.

But the most valuable fact is in any case the observation of Keibel and Mall, who showed that a secondary sex character such as the greater depth of the recto-uterine excavation in females is to be found in the fetus before the primary sex characters (the genital glands) are developed.

The secondary sex characters are therefore associated with the primary not only through the hormonal influence of the glands but also through a chromosomal correlation. In lower animals, for instance in insects, this latter is the only existing, as the hormonal correlation develops later on in the phylogenesis. In insects, no influence of the sexual glands upon the sex characters is to be observed. In higher animals, the genital hormone

stimulates and protects the chromosomal potency to bring about the characteristic sexual signs in the different parts of the organism. But, despite this obvious endocrine function, it must never be forgotten that every cell of the organism obtains its definite sex peculiarity from the moment of fertilization of the ovum, that a certain chromosomal structure is responsible for the sex in every one of the body cells. Of course a sexual difference will not be manifest in the cells of the liver or of the lungs, but it will be quite obvious in the cells that produce the hair, those that form the breasts and so forth.

All the different kinds of intersexuality are to be understood only by the supposition that some developmental malformation, some chromosomal disturbances had taken place some time during the development in certain cell groups. By the interference of those chromosomal anomalies with the hormonal stimuli the different types of intersexuality are to be explained. That such a chromosomal disturbance may happen somewhere during the individual development is much less astonishing than the experience that those disturbances are to be observed so seldom.

Nobody will doubt that a case of real hermaphroditism (possession of testicles and ovaries at the same time) cannot be understood through the assumption of a hormonal anomaly. The development of both sorts of genital glands in a single individual can be the result of a primary chromosomal disturbance only. Using the known formulae of the general science of heredity, we may assume that every female cell has acquired from mother and from father the equal amount of power for developing female and male characters, but that the female power under those conditions is always predominant over the male. A male organism would have acquired from his father only the power to develop male characters and since two male determinants prevail over one female, the evolution goes in the male direction.

The science of genetics and heredity is well acquainted with the fact that the prevailing power of a unit over its so-called allelomorph, in our example for instance the prevalence of F over M, or the prevalence of two M's over one F, is not an absolutely constant and unchangeable fact, but may vary within certain limits and may be dependent on different endogenous or

exogenous conditions. This variability of prevailing power is the real basis of the different kinds of intersexuality. If through an unknown cause in an individual of the female structure (FM) (FM), or of the male structure (FM) (M), the normal predominance of one F over one M, or of two M's over one F, be absent, if both tendencies become manifest and bring about at the same time true female and male characters, then the different cases of intersexuality are the consequence of the chromosomal anomaly. The famous experiments of R. Goldschmidt on butterflies (Lymantria dispar) are the basis for this theory.

Fig. 6. Hemilateral gynecomastia.

The highest degree of intersexuality, the result of an absolute absence of a prevailing relation between allelomorphs F and M, is the real hermaphroditism with testicles and ovaries at the same time. Lower degrees are cases in which disturbances in the sexual differentiation of the organism are due to an insufficient prevalence of the sexual allelomorphs and are to be found only in certain parts of the organism. In those cases only one sort of genital gland has developed and its sexual hormone augments the primarily insufficient prevalence of one sexual principle. Different types of pseudo-hermaphroditism and lower

degrees of intersexuality such as gynecomastia, hypospadias, heterosexual type of crines pubis, homosexuality and so on, are the natural consequence of the interference of the abnormal chromosomal sexual potencies with the hormonal influence of the sexual gland.

The abnormal chromosomal sexual potency due to an abnormal structure or to an abnormal prevailing relation between the sexual allelomorphs need not be generalized as originating from the fertilized ovum but may be present in quite exceptional cases only in certain cell groups of the organism caused by some disorders in the mitotic cell-division during the developmental period. Remarkable is not the possibility of those events but only their rarity, when we consider the highly complicated and minute process of mitosis.

Figure 6 shows a boy of thirteen with a female breast on one side only. Its appearance, shape and consistency is absolutely the same as that of a girl of eighteen. The other side of the boy's chest and the other parts of his organism, especially his genital organs, are quite normal, apart from a marked psoriasis at the knees and a persistent lanugo over the back. The boy shows quite obviously a pronounced heterosexual characteristic, but it is limited entirely to one organ and to one side. It would be quite impossible to explain such a type of intersexuality by abnormal hormonic influence, which could never produce hemilateral effects. Another photograph (Fig. 7) of a male shows an analogous lateral difference in development of another secondary sex character. This man has normally developed hair over the right side of his chest, but has no hair over the left side. Hair on the chest is a marked male secondary sex character, which is in this case developed only on one side and is absent on the other. The man has been observed by my friend Prof. Grote in Halle. I myself saw quite the same hemilateral development of the chest hair in a tuberculous patient at the City Hospital in Buffalo.

Such observations of lateral differences in secondary sex-characters are to be explained only by the supposition of an autochthonous anomaly in the chromosomal apparatus of the concerned cell-groups and never by an endocrine influence; and they illustrate very clearly the necessity of considering the autochthonous sexual constitution of every cell in the same way

as the hormones of the genital glands. They resemble completely some rare observations in animals, especially in birds, in which the animal was on one side male and on the other side a female in every respect. The term "lateral hermaphroditism" has been used for such exceptional malformations.

Thus far we have considered only the co-operation of the chromosomal sexual constitution with the genital endocrine hormone; we have now to add that the cortical part of the suprarenals and probably the pineal gland participate in influencing the sexual differentiation and that the pituitary and thyroid glands and all other endocrine glands may exert some influence upon the development of secondary sex characters by their inter-

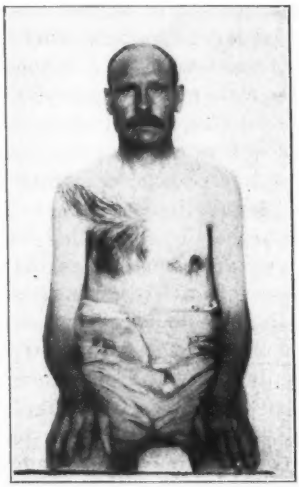

Fig. 7. Hemilateral development of chest hair.

relation with the genital glands. But in no clinical analysis dare the rôle of the chromosomal constitution be neglected. The endocrine organs do not produce, they only influence; they augment or check the chromosomal potency of sexual differentiation.

In the same way as in the origin of the body-length and body-proportions, as well as in the origin of secondary sex characters, the interference of chromosomal and endocrine effects is to be considered in the problem of fat deposition, of evolution

and of senile involution of the organism and in many other problems. Everywhere we meet with the endocrine organs as a sort of multiplier and condenser of certain chromosomal potencies. The continuously increasing complication of differentiation of the cells in the higher organisms during phylogenesis has created a special apparatus for the regulation of certain chromosomal powers, which are present in every cell, but effective only in certain cell-groups. The organs of this apparatus are the endocrine glands and, in part, the nervous system, which directly and through the intermediation of the endocrine organs has acquired an influence upon certain autochthonous potencies of certain cell-groups.

When we recall the fact that in a great number of cases the loss of the endocrine function of the testicles, either by castration, destruction or primary hypoplasia, is followed by a peculiar sort of fat deposition which we call the eunuchoid type, then we must assume that the male genital hormone has a certain influence upon the fat metabolism in quite definite parts of the subcutaneous tissue. It is here of less interest whether a generalized obesity, that is a marked general increase of fatty tissue, is the result of the hypogenitalism or not; the principal point is the affinity of the eunuchoid's or eunuch's fat for certain parts of his body (lower part of abdomen, hips, buttocks, breasts and thighs). The male type of fat-distribution has been transformed into that of the female. We do not observe an analogous change of fat-distribution in a spayed or eunuchoid woman. She may become stout or not, but the fat-distribution is not altered; it remains the same as it was before. According to this observation we must assume that the hormone of the testicles only, not that of the ovaries, exerts a checking influence upon the fat deposition in certain regions of the body; it must check in some way the lipophilia or lipotropia of these places.

The terms lipophilia or lipotropia are not merely useless paraphrases of our observation but they are really existent facts. There are in the literature some very striking clinical observations that prove indubitably the fact of a different lipophilia or lipotropia in different parts of the subcutaneous tissue. Thus, a young girl suffered from a burn on the back of her hand, and the defect had been covered with a transplanted piece of the skin of the lower abdominal region. As the girl grew up, married

and became rather stout, the fatty layer of the transplanted skin at the back of the hand did not increase in the same way as at the symmetrical site in the other hand; but it increased much more—just as much as the subcutaneous fat in the lower abdominal region whence this skin-flap had originated. That is a proof that every place on the body surface has its own specific tendency to capture and fix a certain amount of fat and that this regional lipophilia remains unchanged even after many years in transplanted skin.

The lipophilia of the subcutaneous tissue is a constitutional chromosomal character, but it is influenced by the testicle-hormone. The testicles diminish the lipophilia in certain places of the body, and we can observe that the absence or insufficiency of their function is associated with the female type of fat-distribution. The knowledge of this fact seems to be particularly important in cases of infantile obesity—fat boys before puberty show generally this female or eunuchoid type of fat distribution, as the endocrine influence of their testicles upon the lipophilia of the subcutaneous tissue has not yet developed. It is quite wrong to refer, as has been customary, in those cases of infantile obesity to a genital or perhaps primary pituitary origin of the obesity on account of this particular fat distribution. The genital organs may develop later in time and functionate quite normally, but as long as they were not yet functioning and therefore not yet checking the lipophilia at definite places on the body-surface, the fat distribution follows as a rule the feminine, eunuchoid—or better—asexual type.

On this occasion I should like to mention that the different types of fat distribution in grown-up females are not at all due to different endocrine disorders or to different functional activities of the endocrine glands, but are due solely to the different constitutional, chromosomal lipophilia of the body-areas. I am obliged to emphasize this fact in opposition to a considerable number of authors, who attribute different types of fat-localization to different endocrine types, for example, to a hypogenital or to a hypopituitary state. There does not exist a single proof for this supposition.

I have separated especially four main groups of female fat-distribution due to differing chromosomal lipophilia of the spe-

cial parts of the body-surface. By far the majority of women belong to the first group which I have called the "Rubens-type" and which is characterized by the predominance of fat localization in the lower abdominal wall, hips, loins, buttocks and thighs. The second group I have called the "breeches-type"; this type has its fat chiefly or exclusively in the trochanteric region of the thighs. The third group exhibits a marked contrast between the rather stout superior part of the body (thick arms, neck, and fatty breasts) and the thin abdomen, pelvic region and legs. The fourth type on the contrary has disproportionately stout legs and hips associated with a thin upper half of the body. Some special subtypes are represented by women with disproportionately fatty breasts or with the so-called steatopygia (extremely stout buttocks), a common racial character in some negro races.

These different types of fat distribution are not due to different endocrine constellations, but certainly depend upon a different regionary lipophilia of the subcutaneous tissue. Whether a woman should get stout or not may be partially due to her endocrine constellation, but whether the fat is distributed on the body-surface according to the first or one of the other types—that is determined solely by the autochthonous chromosomal lipophilia of the special regions.

Though I said that the development of an obesity *may* be due to an endocrine disorder, it must be added that the same kind of endocrine trouble is not always followed by the same clinical consequences and particularly not by the same degree of obesity. There are cases in which castration in a female produces a marked obesity, but I know of other cases in which no increase of weight has occurred after the removal of the ovaries. Especially do I remember a mother and her daughter who had both lost their genital glands by operation on account of a cystic degeneration of both ovaries; not only did they fail to develop any obesity, but both became markedly emaciated after the operation. It is not a single endocrine gland only, but the total of all of them combined with the constitutional chromosomal reactivity of every body cell that determines the consequences of an endocrine trouble and determines the varying clinical symptomatology following such an endocrine disturbance.

We know of a pathological state designated "progressive lipodystrophy," which is to be understood only by assuming a pathological relation and change of the lipophilia of different regions of the body surface. Such cases are characterized by a marked decrease (up to a complete disappearance) of the fatty tissue in the superior half of the body, especially in the cheeks, associated with an increasing obesity limited to the legs, hips and buttocks. Neither characteristic nor always identical endocrine changes are to be found in these cases, and when some endocrinopathic features are present, they are certainly not the cause of the pathological condition of the fatty tissue but are concomitant signs of a more generalized abnormal chromosomal structure, or, briefly, of an abnormal individual constitution.

The most interesting examples of interference of chromosomal with incretory influences are to be observed in the clinical pathology of development and involution of the body. Insufficient function of the thyroid, pituitary, genitals, and thymus at an early age is associated with developmental anomalies, with the persistence of certain infantile characters, but all of these cases are by their special symptomatology different from the rare cases of generalized hypo-evolution of so-called "universal infantilism." Just as a child does not differ from an adult by mere endocrine insufficiency of one or more glands, so universal infantilism is not due to a primary endocrine trouble but to a general cessation of development affecting every cell of the body. The hypoplasia of the endocrine organs is in those cases not the cause of the infantilism but a part of the general hypoplasia.

We know of a special type of dwarfism that is certainly also not due to an insufficient function of one or of several endocrine glands, although an early insufficiency of the thyroid as well as of the pituitary or the thymus can give rise to a type of undergrowth or dwarfism. But the so-called "primordial dwarfs" (v. Hansemann) are creatures whose single anomaly is their smallness. They are in every respect well and proportionately developed, show proportionate genital organs with normal function, are of normal intelligence and look like a miniature of a normal individual. Qualitative trouble is absent entirely. Primordial dwarfism is always hereditary and in certain negro races it is a racial characteristic. There can be no doubt that it is not

an endocrine anomaly, but only a chromosomal anomaly of the whole organism that is the real cause of this peculiar kind of dwarfism.

Certain units are to be assumed as regulating the qualitative evolution as well as the quantitative growth of the organism. An anomaly of these units brings about sometimes universal infantilism, sometimes primordial dwarfism. As these special units for evolution and growth are effective particularly on certain endocrine glands whose function is somewhat like a lubri-

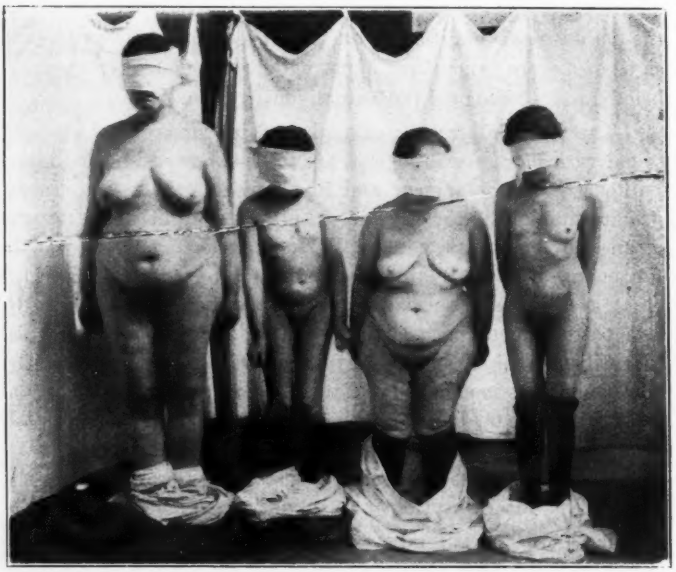

Fig. 8. Family with different kinds of growth trouble.

cant and multiplier of these units, we shall not be astonished to meet with the most different kinds of trouble, due partially to a generalized chromosomal and partially to an endocrine insufficiency. This view alone can elucidate a great number of the disturbances of growth and evolution met with in daily practice. Of particular interest in this respect are some observations on alternation of the different types of evolutionary and growth troubles in different members of one family, revealing the existence of a primary chromosomal anomaly.

P. Stewart, for instance, describes a young man of twenty affected with a general myoclonia. His growth had been completed at fourteen. Though his genital organs developed, the hair remained infantile. One sister of this patient did not grow any more after her twelfth year, but menstruated regularly after her fourteenth year; five brothers and sisters were born prematurely on account of their quite abnormal size at birth. Observations of partial or universal gigantism in one member, and of dwarfism, of acromegaly, of eunuchoidism and of other endocrine disturbances in other members of the same family have been described several times in the literature. Certain endocrine glands seem to be, in those families, points of lowered resistance and show a marked tendency to be affected either by neoplastic or, as certain observations illustrate, even by a tuberculous process.

Fig. 8 shows a mother with her three daughters. The first (from the left side) is a daughter of normal size and development. We may observe the identical kind of fat deposition (especially the cuff-like fatty masses over the wrist) in the daughter and in the mother (the third from the left in the picture), who represents a chromosomal type of dwarfism. The second from the left is a thirty-nine-year-old daughter with a pituitary and chromosomal dwarfism who exhibited an extreme degree of genital hypoplasia, eunuchoid body proportions, absence of secondary sex characters and amenorrhoea. The third daughter on the right is to be diagnosed as a chromosomal undergrowth with some features of rickets.

Fig. 9 shows a pituitary dwarf seventeen years old, an identical twin whose brother is affected by the same kind of disturbance of growth and evolution. The chromosomal character of this pituitary anomaly is therefore quite indubitable.

Very interesting is also an observation of Dr. R. Wagner at Prof. Pirquet's Children's Clinic in Vienna; he describes two brothers at the age of three and three and a half years, respectively, both affected with a marked premature development, corresponding to a precocious puberty. As signs of an intracranial and especially of a pineal lesion as well as of a suprarenal anomaly were not to be detected, a chromosomal anomaly, more or less

limited in its manifestation to the genital organs, is to be assumed in those two brothers. Although in certain cases of premature development a primary pineal or suprarenal disorder may be the cause, we have to consider the cases, in which either marked changes such as aplasia of pineal had been present without a premature development or in which a precocious puberty appeared apart from any pathological condition of the pineal gland (Krabbe). The observation of the Viennese Children's Clinic illustrates in an obvious way the constitutional chromosomal character of some cases of this developmental anomaly.

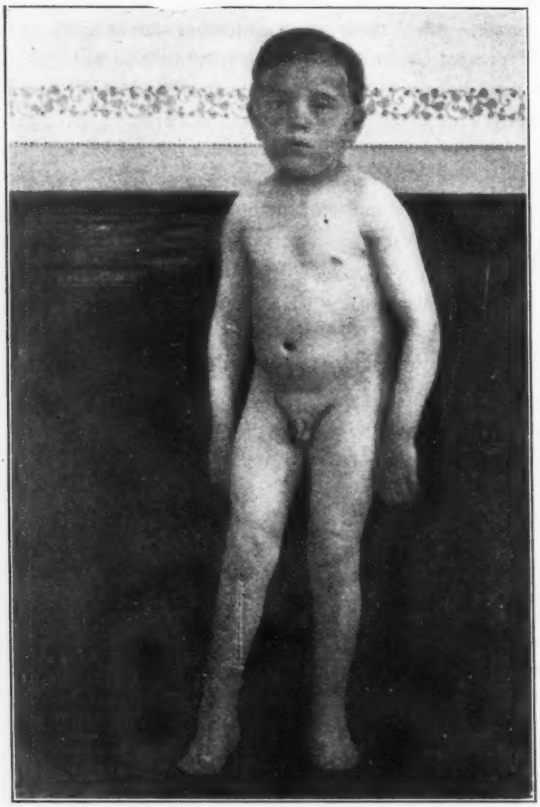

Fig. 9. Pituitary dwarfism in an identical twin of 17 years.

Senile involution takes place in every body-cell to a certain degree; it appears sometimes earlier in one part, sometimes in another part, of the body. It is due to a primary constitutional chromosomal character of the organism. The special type of general senescence, however, is in a high degree dependent on the special endocrine glands, which are subjected to senile involution in a particular way.

We may distinguish two main types of senile involution. One, the dry, atrophic, emaciating type, shows quite a different general appearance from the second, in which a more or less marked obesity develops, in men usually of the eunuchoid, feminine or asexual kind of fat distribution over the body surface. We may assume in this latter type a predominating senile atrophy of the genital and thyroid glands modifying and molding the general appearance, whereas the first type of general senescence will bring to our mind rather the suggestion of a prevailing senile atrophy of the pituitary gland, when we recall the rather obvious resemblance of these dry, emaciating old people with the so-called pituitary cachexia described for the first time by Simmonds. Anatomical investigations on this subject are being carried out by my collaborators in Vienna at the present time.

I have tried to recall to your memory the importance and high power of the chromosomes and their constituents, to show that the endocrine glands generally are only, as it were, condensers or multipliers of certain chromosomal potencies, and that not everything which may be attributed today to pure endocrine disturbances is, in reality, of endocrine origin. The interference of general chromosomal (i. e., constitutional) and of incretory influences is to be taken into consideration in the greatest number of cases where up to date unsatisfying hypothetical suppositions of pure hormonal trouble usually are to be met with.

A practical consequence I have drawn from these theoretical views may be mentioned, although the experiments have not yet been carried out far enough to be conclusive. If the chromosomes are the primary substratum of the potencies for growth and evolution, then it may be possible to transmit this marvellous high power to an organism whose power is in this respect

deficient. I tried to utilize this power in the maximal degree obtainable from fetal organs, and am now treating in Vienna cases of dwarfism and infantilism with extracts of fetal organs, partly from fetal calves, partly from human fetuses. Up to date these experiments seem to be yielding satisfactory results. I may add that Carrel and his pupils add to their culture media, upon which they grow the different body-tissues in vitro, embryonic extracts as a stimulus.

PHAGOCYTOSIS IN TOXIC GOITRE

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I

The presence of scattered lymphocytes and even well-defined lymphoid nodules in exophthalmic or toxic goitre is very well known. Simmonds (1) traced them in about 80 per cent of the cases examined, while Kocher (2), in his classical work, discussed at length their presumed origin and considered them as being attracted in the diseased gland by the alteration of the colloid. Mallory (3) came to similar conclusions and insisted on the phagocytic power of the lymphocytes toward the altered colloid. Quite recently, again, Troell (4) found lymphoid infiltration in 90 per cent of the diffuse, toxic goitres examined by him. However, the existence of marked phagocytosis of the actively working thyroid cells themselves is a fact which seems to have been overlooked.

My purpose is to draw attention to this particular point and to give an accurate description of the different stages of the process by referring to the figures accompanying this paper.

To begin with, small lymphocytes break through the connective framework (c, Fig. 1) surrounding an apparently active secreting thyroid alveolus (l, Fig. 1), and lodge at the bottom of the cells. In Fig. 1 is seen a very striking feature of a lymphocyte (l) with elongated and twisted nucleus disarranging the connections of the glandular cell and repelling the latter into the lumen. Desquamation is—at least in this instance—the result of the invasion of lymphocytes.

When these elements occur in greater number, the connective lining of the vesicle is resorbed at places (Fig. 2). The increase of the phagocytic power of the lymph cells is proved by the fact that they acquire a larger amount of dark, basophil protoplasm and all of the characteristics of the phagocytic plasma cell with its wheel-like nucleus (pl, Fig. 2). The effects of their functional activity can be followed now, step by step.

ABBREVIATIONS

a.T.A., altered thyroid alveoli.
a.T.c., altered thyroid cell.
coll., colloid.
d.c., desquamated cell.
e., connective frame work.
g.T.c., giant thyroid nucleus.
l., lymphocyte.
l.u., lumen.
p.l., plasma cell.
T.A., thyroid alveoli.
t.b., terminal bars.

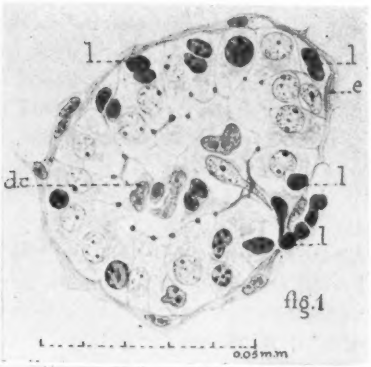

fig.1

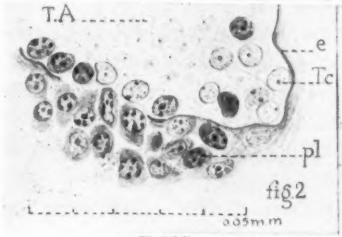

fig.2

fig.3

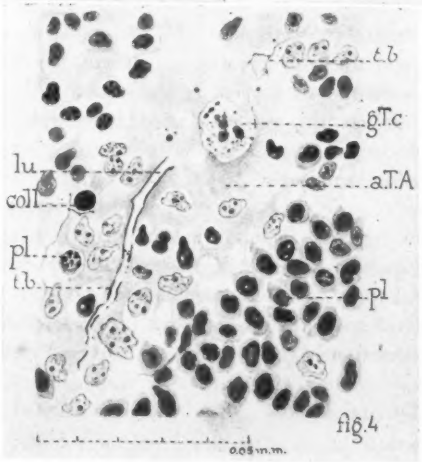

fig.4

The protoplasm of the thyroid cell disappears gradually. As a result of this cytolysis, a colorless halo separates the phagocytic from the glandular cell. Very soon also the nucleus of the thyroid cell gives evidence of progressive alteration and it loses its spherical shape; the nuclear membrane becomes wrinkled and in the end disappears altogether. Pycnosis and karyolysis are the final stages (Figs. 3-4). Yet, in these phagocytic acini giant nuclei sometimes exist (g.T.c, Figs. 3-4), but most of them become irregular in shape and poor in a sort of condensed and scattered chromatin (g.T.c, Fig. 4).

These degenerative processes alter deeply the normal architecture of the thyroid vesicle. Cellular limits can no longer be traced and the protoplasm appears as a structureless mass, vacuolized or disintegrated in places (Figs. 3-4). At such an advanced period as is represented in Fig. 4, it would even seem difficult to recognize in these altered elements previously secreting thyroid cells. Yet a careful examination makes clear that such is the case. The most decisive criterion in establishing their identity is the existence of terminal bars (t.b., Fig. 4) which seem to remain present in about 50 per cent of thyrotoxic goitres according to Troell (4). Our preparations show that they resist phagocytosis a long time, and that they prove most useful in identifying the badly damaged thyroid acini. In other instances, the presence among the cells of a small, compact mass of colloid, intensely stained by iron hematoxylin, is another way of ascertaining the thyroid nature of the degenerated cell masses (coll, Fig. 3). However, the presence of this basophil colloid, although very frequent, is by no means constant.

Complete destruction of the thyroid cells is the end of the whole process. Large areas of previously hypertrophic thyroid tissue are now replaced by a diffuse infiltration of lymph cells, among which scattered and altered thyroid elements can be identified here and there. It now remains to show in what pathological variety of goitre the transformations described above can be seen, and then to analyze what kind of thyroid cells undergoes phagocytosis.

II

The amount of material in which I discovered the alterations referred to is very small indeed. It consists of two speci-

mens of toxic goitre—the only two I have had opportunity to examine since I took the direction of the department quite recently. Still, the facts are conclusive enough to be published and the data given here may be of some use to other investigators working on a more extensive scale. Figs. 1 and 2 belong to a clinically true exophthalmic goitre in a woman forty-five years of age, operated on a year and a half after the onset of the symptoms. Ligation of the arteries was performed previous to thyroidectomy. The pathological aspect of the goitre is of the type which Wilson (5) would classify as an advanced primary hypertrophic and hyperplastic goitre. In fact, it corresponds to the classical image reproduced in our modern textbooks [vide Mallory (3), MacCallum (6), P. Masson (7)].

Big lymph nodules are present. Yet I want to draw attention to two particular features: degenerative changes of the thyroid vesicles without any sign of phagocytosis can be traced, but very seldom; there are, on the average, one or two acini every ten sections of one square inch surface. They are quite different from any of the acini shown in our drawings. On the other hand, close to the big vessels exist lumenless tubules of the embryonic type. We consider them as composed of reserve cells to be compared, for instance, to those of the glomerular zone of the suprarenal cortex. They turn gradually into large, secreting cells.

Figs. 3 and 4 have been drawn from a diffuse (exophthalmic?) toxic goitre in a woman forty years old. The disease began after recovery from influenza about a year ago. Rest-cure and Moebius serum greatly improved the patient's condition, according to the surgeons' report. However, relapse occurred six months later; thyroidectomy was performed without any previous ligation of the arteries. I could not ascertain that this case corresponds to the accurate conception of true exophthalmic goitre emphasized by Plummer (8) and Wilson (5). I do not know whether the required tests have been performed, yet we can certainly consider it as a severe toxic goitre.

On section, the removed gland looks pink, but shows here and there colloid nodules about 0.5 cm. in diameter. Microscopically, this diffuse goitre is composed of fairly regular-shaped acini—spherical or ovoidal—the size of which offers great

variations. The striking features of this goitre are the complete absence of foldings of the epithelium or papillary projections into the lumen, the larger dimensions and the cubical rather than columnar shape of the cells and the presence of a thick basophil colloid in a great number of the alveoli. Mitochondria are extremely abundant in some of the acini. Mitotic figures can be detected. In strong contrast with those active zones appear, in sections, the circular areas of colloid regression with their distended acini and flattened epithelium.

III

The question arises as to what kind of thyroid cells undergoes phagocytosis. First let us remark that the existence of a phagocytic process has nothing to do with the previous ligation of arteries. In fact, it is more pronounced in the goitre where no preliminary tying of vessels was performed.

On the other hand, the thyroid acini showing types of regression such as described, for instance, by Ribbert (9), are, generally speaking, not affected by the phagocytic process. The same is true of the colloid areas.

Lymphoid infiltration is most marked in the neighborhood of big vessels and just there are located the small and least differentiated thyroid cells, tubules or acini. The lymph or plasma cells attack especially those small acini that are just turning from the tubular into the alveolar form. Yet, middle-sized, spheroidal acini, provided with high epithelium, can undergo the same process, but never to the same extent or frequency.

Newly differentiated acini show every sign of functional activity. In both goitres examined they give most striking evidence of richness in granular or ring-like mitochondria derived from the rod-like ones of the resting period. Big nuclei, turgescent but quite regular and double the average diameter, can be seen inside and on the border line of areas where phagocytosis takes place. That this enlargement of nuclei is not a pathological consequence of the dense lymphoid infiltration seems proved by the fact that these nuclei are found sometimes—though in much smaller numbers—in non-infiltrated areas. These nuclear and protoplasmic peculiarities show that phagocytosed areas are composed of very active thyroid cells.

However, hyperfunction of the glandular cells is not the only reason for attraction of the lymph cells, since it is evident that the larger, hyperplastic acini provided with papillary projections into the lumen and also very active, do not undergo phagocytosis at all. Qualitative influences must intervene of which we have, unfortunately, but little objective data. Small acini with basophil colloid are attacked as well as those containing a more fluid secretion stained by eosin or light green. The reaction of the colloid with Azocarmin (Mallory) and its relationship with phagocytosis has not been investigated. This would seem to be a promising field for research, in view of the data given by Troell (4) concerning discrimination of the thyroid secretion. It is concluded that *only those thyroid acini undergo phagocytosis which are newly differentiated and are at a special stage of functional overactivity.*

Is phagocytosis a constant phenomenon in exophthalmic or toxic goitre? This question can be answered better by those to whom more abundant material is available. Now that attention has been called to the process, it is possible, for instance, that, judging by Goetsch's (10) microphotographs, it will be easily detected in goitres which that author calls "diffuse adenomatosis."

It is not our intention to dwell on the biological significance of phagocytosis in toxic goitre. Evidently it is a defensive process which may be, perhaps, compared with Murphy's (11) and Rubens Duval's (12) lymphoid reaction in tumors. The chemical nature and the toxicity of the cell-metabolism products are probably the underlying causes of the phenomena described here. Our findings seem to indicate that these observations give support to the dysthyroidism theory of exophthalmic goitre, but it would be unwise to draw such a general conclusion from the small amount of material here investigated.

SUMMARY

1. Besides the well-known lymphoid infiltration in toxic and exophthalmic goitre, there is a marked phagocytosis of thyroid cells. The different stages of the process are described.

2. Phagocytosis is seen in toxic goitres of different pathological aspects, both in the one showing so-called primary hyper-

trophy and in another showing, besides active lobes, degenerative colloid areas.

3. Only those thyroid acini undergo phagocytosis that are newly differentiated and give evidence of great functional activity.

BIBLIOGRAPHY

1. Simmonds, M.: Deutsche med. Wchnschr. (Berl.), 1911, **37**, 2164.
2. Kocher, A.: Virchow's Arch. f. path. Anat. [etc.] (Berl.), 1912, **208**, 86.
3. Mallory, F. B.: Text-book of pathology. W. B. Saunders, 1918; Principles of pathological history. W. B. Saunders, 1914.
4. Troell, A.: Arch. f. klin. Chir. (Berl.), 1923, **124**, 700.
5. Wilson, L. B.: Am. J. M. Sc (Phila.), 1913, **146**, 781; ibid., 1914, **147**, 344.
6. MacCallum, W. G.: J. Am. M. Ass. (Chicago), 1907, **49**, 1158.
7. Masson, P.: Diagnostics de laboratoire. Maloine, Paris, 1923.
8. Plummer, H. S.: Am. J. M. Sc. (Phila.), 1913, **146**, 790; Med. Rec. (N. Y.), 1919, **95**, 1074.
9. Ribbert, H.: Virchow's Arch. f. path. Anat. [etc.] (Berl.), 1915, **219**, 246.
10. Goetsch, E.: Endocrin. (Los Angeles), 1920, **4**, 389; ibid., 1922, **6**, 59.
11. Murphy. Congr. Internat. du Cancer, Strasb., 1923; July 23, 24; abst., Presse méd. (Par.), 1923, **31**, 737.
12. Rubens Duval: Contr. Internat. du Cancer, Strasb., 1923, July 23, 24; abst., Presse méd. (Par.), 1923, **31**, 736.

SOME FAVORABLE EFFECTS FROM THE ALIMENTARY ADMINISTRATION OF INSULIN*

(Preliminary Communication)

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The desirability of finding a satisfactory method for oral administration of insulin requires no argument. In July, 1922, some observations (1, 2) on the absorption of the hormone after the instillation of a crude extract into the human duodenum were made. But the method is obviously impracticable as a routine practice in the treatment of diabetes. Since that time we have tried several other methods. Many of our attempts failed altogether, some were quite equivocal in their results, and a few were apparently so clearly positive that they should be placed on record even though the experiments at this time are incomplete.

Insulin is rapidly destroyed by pepsin (3, 4) if given sufficient time in the stomach or if not protected in some way against its action. It is also rapidly destroyed or inactivated in tryptic digestion (3, 5). Both of these results have been repeatedly confirmed in this laboratory. The problem, then, is to find a means of circumventing these destructive agents. In duodenal administration only one of these agents needs to be evaded and this apparently was accomplished in our observations by the simple expedient of leaving the extract acid with hydrochloric to the extent of from 0.1 to 0.2 per cent. Alcohol also was added with the idea of increasing the chances of absorption.

Another possible means of defeating or escaping the destructive action of pepsin seemed to be the administration of large volumes of slightly acidified extract in the hope that some of it would be evacuated from the stomach before pepsin had a chance

*Read at a meeting of the Western New York Branch of the Society for Experimental Biology and Medicine, February 16, 1924.

to diffuse throughout the solution. This was tried up to the limit of 3 liters of the extract daily. It was given as a broth both hot and cold. Some of the broth was sent also to several of the larger clinics. The results were nearly uniformly negative.

Next, in the hope that a still more concentrated solution than our first filtrate might be efficacious, the insulin was precipitated together with some protein by our usual method of saturation with sodium chloride (6), and the precipitate taken up in a much smaller volume of acidulated water. This gave positive results on both partially and totally depancreatized dogs (Table 2), showing that it had passed the stomach successfully. It was then tried on several human subjects with, at first, encouraging results (7). Examination of the same patients after a somewhat longer period, however, showed that the alimentary tract had apparently adapted itself to the higher concentration and succeeded in destroying the hormone. Chart I illustrates the successive increases in dosage which were necessary to produce a lowering of blood and urine sugar.

Even before this, desiccated material obtained by acetone precipitation of insulin from crude extract and drying was tried, but with disappointing results.

We then tried alcoholic solutions by stomach, and although positive evidence of absorption, both in the normal rabbit and in partially depancreatized dogs, could be obtained in agreement with Winter (8), the results with human patients to date have not been satisfactory. This is confirmed by Salèn (9).

Finally enteric coated capsules and tablets were tried. Small gelatin capsules were filled with dried insulin material obtained from our salt precipitate, and were coated over with salol. The salol coated capsule was enclosed in a larger gelatin capsule. After several trials with dogs and patients it was found that the salol coating disintegrated often in artificial gastric juice and sometimes withstood artificial tryptic digestion for several hours. In a few instances, however, notwithstanding these results in artificial digestion, the salol coating seemed to accomplish the result *when the capsule contained in addition to insulin a harmless substance calculated to delay the action of trypsin* temporarily in the immediate neighborhood of the capsule when it went to pieces in the intestine.

This method was then improved by having more perfect enteric coatings prepared for us by reputable pharmaceutical manufacturers and it is this form of tablet which has encouraged us to make a preliminary report of some favorable results of enteric administration of insulin.

The exact methods of enteric coating are unknown to us; but in artificial gastric juice the shell withstands digestion for

TABLE 1.

TESTS ON HUMAN SUBJECTS.

Patient	Date	Amount and No. of Extract	Drop in Blood Sugar (mgm.)	Hours	Drop in Urine Sugar in 24 Hours (gms.)	Remarks
Bu[1]	1922	DUODENAL ADMINISTRATION First blood before breakfast.				
	July 6- 7	360 cc. No. 25 (2) + 0.1% HCl	61	11	22	
	8- 9	400 cc. No. 33 + 0.2% HCl	40	2⅓	20	
	15-16	250 cc. No. 39 (1) + 0.1% HCl	40	2	34	Following 250 cc. 0.3% Na_2CO_3.
	18-19	500 cc. No. 41 (2) with 6% alcohol	60	4	8	
	20-21	1000 cc. No. 49 (1) with 6% alcohol	60	4¼	34	2 doses 3½ hours apart.
Bl	18-19	500 cc. No. 45 (2) with 8% alcohol	101	6	16	Patient intoxicated.
	22-23	500 cc. 5% alcohol	36	3	7	A. M.
		500 cc. No. 48 (2) with 5% alcohol	42	5½	13	P. M.
	25-26	700 cc. No. 46 (1) with 5% alcohol	53	8½	6	
	27-28	1000 cc. 5% alcohol	34	8½	1.1	
	29-30	800 cc. No. 46 (1) no alcohol	42	9¼	5.0	
	1923	STOMACH ADMINISTRATION OF ENTERIC COATED TABLETS—Constant diet.	Bl. sugar level mgm.		Sugar excretion 24 hrs. gms.	
E. V.	Nov. 8	30 units insulin subcut. and 6 tablets daily	50		Sugar free	
	9	30 units insulin alone	142		Sugar free	
	1924					
E. M.	Jan. 7-12	6 to 12 tablets daily, Jan. 7.	500		61.6	Both blood and urine had been on increase previous to use of tablets.
		Steady drop to Jan. 12	265		13.7	
	15-19	16 tablets daily, Jan. 15	344		42.7	
		Steady drop to Jan. 19	303		19.8	

[1]This case is reported from Highland Hospital by the courtesy of Dr. John R. Williams.

at least three hours and opens up within 15 to 30 minutes in artificial tryptic digestion.

For delaying temporarily the action of trypsin and thus affording an opportunity for the absorption of insulin we fol-

lowed the hint obtained from direct duodenal administration, namely, of introducing with the insulin material weakly acid substances in varying proportions. Several weak organic acids which naturally occur to one for this purpose are: citric, malic, tartaric acids, etcetera, and weakly acid salts such as sodium dihydrogen phosphate. All of these have been tried with, as yet, no clear advantage of one over the others.

Table 1 presents a few positive tests on human subjects: (1) of duodenal administration and (2) of administration of enteric coated tablets containing acid substances.

The efficacy of duodenal administration can scarcely be doubted; for in addition to evidence of effects upon blood sugar and urinary excretion of sugar, the patients, both being cases of severe type, experienced improvement in clinical appearance and muscular strength and showed some gain in weight. With alcohol there was a little greater effect on the blood sugar though scarcely upon excretion, and there was some effect on both with alcohol alone (10). The four tests with extract alone in weak acid prove, we think, that insulin can be absorbed from the human gut without the aid of alcohol. That the acid alone could not have caused the effects either directly or through delay of intestinal digestion is strongly indicated by the fact that even small doses of hydrochloric acid increase the output of sugar and depress the respiratory quotient in depancreatized dogs (11). Haemaglobin tests with patient B1 showed that the effect on blood sugar could not have been due to dilution.

With regard to case E. K., shown in Chart 1 but not in the table, it should be explained that the boy was purposely placed upon a diet somewhat above his tolerance because his parents were very desirous that he should gain weight rapidly during the summer months so that he could enter school in the fall. During the period of observation in the hospital, represented by the chart, he was on a constant diet, and the sugar in both blood and urine was increasing from day to day before administration of the broth was started. The very first dose containing 72 rabbit units produced a satisfactory reduction in both, but this amount soon became ineffective. Only when resort was had to the salt precipitate and the dosage increased to 300 rabbit units was the next reduction accomplished. When the second day at this level showed no further improvement the dose was

increased to 600. Again a reduction occurred the first day, but did not persist the second. Broth in the original dosage was then tried, but was wholly ineffective. Salt precipitate in amounts up to 800 rabbit units later did not produce so great an effect as originally had been produced by much smaller doses.

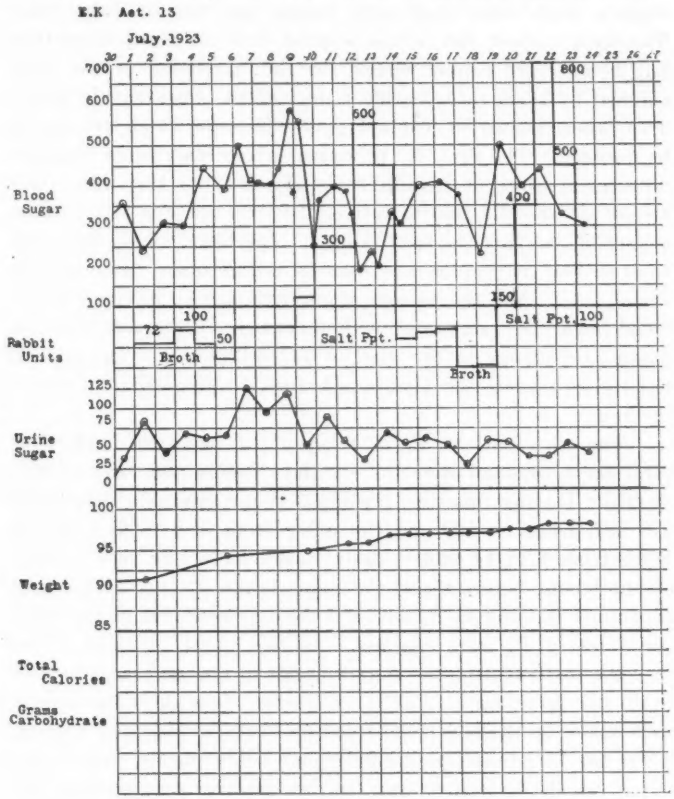

Chart 1. Case E. K., age 13. Showing increasing dosage of salt precipitate necessary to produce effects on blood sugar and urine sugar.

There seems, then, to be evidence in this chart of rapid adaptation in the secretory mechanisms of the alimentary tract to meet the exigencies presented by such material.

The boy's weight gradually increased throughout the period because his tolerance was sufficient to handle the necessary

caloric intake, and he suffered no harmful effects so far as could be noted. The experiments with stomach administration were stopped as soon as it was clear that his tolerance could not be substantially improved by this method.

The first enteric coated tablets containing insulin and organic acids were used with human patients in July, 1923. Two such subjects not in the hospital were rendered sugar free, but because we cannot vouch for the constancy of the diets claimed by them no scientific report of the cases can be made. Two others shown in Table 1 gave reactions which are not to be doubted. The first, E. V., was a severe case which required 30 clinical units of insulin subcutaneously to keep the urine free of sugar. Six tablets were added with the idea of replacing a part of the subcutaneous dosage. The blood sugar, however, went so low (it remained at near 50 milligrams, "fasting," for three days) that the tablets were withdrawn; whereupon the blood sugar next day rose, without change in the subcutaneous dosage, or change in the diet, to 142 milligrams. The patient left the hospital a few days later before it was possible to repeat the test.

The other patient, E. M., a boy of 13, had been in the hospital on a constant diet for six days before the tablets were started. During this time the blood sugar gradually rose from 275 milligrams to 500 and the urine from 38.5 to 61.6 grams. With from 6 to 14 tablets daily, taken in lots of two to four, one-half hour before meals the sugar began at once to fall and continued steadily to do so until the levels shown in the table for January 12 were reached. At this point, in spite of an increase to 16 tablets, the sugars began to rise and continued so to do for three days. For the following four days the tablets were taken by the boy while lying on his right side and sipping water for 15 minutes to one-half hour before meals. This technique which is well known to be effective for passing the duodenal tube seemed to be effective also in securing prompt passage of the tablets into the duodenum. At all events the decline in both blood sugar and urine sugar was continuous to the levels indicated in the table for January 19. Increasing the tablets to 32 per day did not have any further effect, possibly because they contained sufficient carbohydrate to offset the favorable effect of the insulin. These particular tablets were coated

with milk sugar and contained also a small amount of starch necessary for compacting the material. The boy left the hospital and although he has received since that time other tablets of the same general nature which seemed to act favorably no accurate report of the effect can be made.

TESTS ON DIABETIC DOGS

In Table 2 are given a few favorable effects upon depancreatized dogs. All these animals had been under observation and control as regards diet for at least two weeks following

TABLE 2.
TESTS ON DEPANCREATIZED DOGS.

Dog No.	Date 1923	Amount of Extract	Drop in Blood Sugar (mgms.)	Hours	D:N	R.Q.	Urine Sugar (gms.)	Remarks
47 Partial	June 28	9:35 A.M. 450 cc. No. 14, broth	32	5				Dog fed meat diet every day same.
		10:10 same						
	29	900 cc. No. 17 broth	17	6	2.52			
	30				1.86			
	July 10	100 R. U. salt ppt. No. 17	(212)		2.28			
	11	100 R. U. salt ppt. in sol.	47 (165)	24	2.34			
			11 (150)	24	0.0		Sugar free	
54 Partial	Oct. 8	4 enteric capsules	32	5½			10.10	Food same.
	9						1.09	10/6 to 10/10.
	18	3 enteric capsules	63	24	1.90			Food same.
	19				1.00			10/15 to 10/20
51 Total; two weeks after operation	June 27	200 R. U. No. 16 salt ppt. in sol.			2.70	0.699 0.709	5.03	Food constant..
	June 28	200 R. U. No. 16 salt ppt. 40 gm. glucose				0.829 0.765 0.781 0.885 0.825 0.721	11.18	
	June 29	20 gm. glucose				0.951 0.958 0.898	15.84	
				Alcohol	check	0.647 0.647		
	June 30	20 gm. glucose				0.801 0.816 0.800	Sugar free	

operation before the experiments here reported were made. The "broths" used with dog No. 47 were obtained by simple aqueous extraction and contained at the time of administration only a small amount of HCl (pH 4.0). The fall in blood sugar is not great, but taken in conjunction with the decline in the

D:N while the diet remained constant, it can be regarded only as a positive effect of insulin; for the dog was fed only in the evening after the observations on the blood had been completed. In order to increase the dose of insulin without increasing the volume intake of fluid, the insulin was precipitated together with some protein from the aqueous extract and the precipitate containing some 100 rabbit units was dissolved in 200 cc. of water. The first dose produced a fall of 47 milligrams in the morning blood sugar for 24 hours but did not reduce the D:N ratio. In fact, both the sugar and nitrogen were increased on account of the protein contained in the salt precipitate. The next day, however, the blood sugar taken at the same hour was still lower and the urine was entirely sugar free. The effect could not have been due to any injurious effect of salt contained in the salt precipitate, for its amount was very small. Nor could it have been due to any tendency of the pancreatic fragment to resume its function; for the diabetes became steadily worse, and later could not be controlled by stomach administration of salt precipitate. Twice after this the urine became sugar free, but the effect was not so clear cut as in this instance.

With dog No. 54 the enteric capsules, containing dried salt precipitate and a substance designed to delay tryptic destruction of insulin, similar in composition to the tablets employed with the human subjects were used. In the first test four such capsules lowered the blood sugar 32 milligrams in 5½ hours and produced a drop in urinary excretion of sugar for the 24 hours of 9 grams. In the second test the drop in blood sugar was 63 milligrams for 24 hours. The D:N ratio is only approximately correct.

The most conclusive proof of absorption of insulin was obtained with the totally depancreatized dog No. 51. The dog was certainly diabetic as proved by the high blood sugar, the Minkowski D:N ratio on a meat diet two weeks after pancreatectomy and the perfectly typical diabetic respiratory quotient. Two doses of the salt precipitate in water amounting to 200 rabbit units each, one on the 27th and the other on the 28th, followed by 40 grams glucose by stomach tube, produced within a few hours after glucose respiratory quotients well above the diabetic level, and a utilization, assuming the same D:N ratio, of nearly thirty grams of glucose in 24 hours. The

D:N ratio could not be accurately determined because of the unknown amount of protein in the salt precipitate. The next day the quotient went even higher after glucose and the following morning the urine was sugar free in spite of the 20 grams glucose given. An alcohol check experiment on the 30th proved that the apparatus was working properly, and the dog's R. Q. after a third dose of glucose indicated continued combustion. The dog of course had no pancreatic juice, hence the insulin was not destroyed by trypsin. There was at no time any sign of overdosage of insulin, due, no doubt, to its excretion through the urine (12).

CONCLUSIONS

The observations here reported prove, we think: (1) that insulin in crude solution containing 0.1 per cent HCl, placed directly in the duodenum of the diabetic patient, can be absorbed and can function to cause the utilization of sugar; (2) that insulin placed in enteric coated tablets containing a substance designed to delay temporarily the destructive action of trypsin can survive the stomach in some patients, can be absorbed in the intestine, and can operate to improve the diabetic condition very materially.

The practicability of these methods of administration cannot be vouched for in all cases, but it would seem that in many cases they might be used at least to relieve the tedium of frequent hypodermic injections of more refined products.

BIBLIOGRAPHY

1. Sutter, C. C., & Murlin, J. R.: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1922, **20,** 68.
2. Murlin, J. R.: Endocrinol. (Los Angeles), 1923, **7,** 519.
3. Dudley, H. W.: Biochem. (Liverp.), 1923, **17,** 376.
4. Murlin, J. R., Clough, H. D., Gibbs, C. B. F., & Stokes, A. M.: J. Biol. Chem., 1923, **56,** 253
5. Witzemann, E. J., & Livshis, L.: J. Biol. Chem. (Balt.), 1923, **57,** 425.
6. Allen, R. S., Piper, H. A., Kimball, C. P., & Murlin, J. R.: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **20,** 519; also Kimball, C. P., & Murlin, J. R.: J. Biol. Chem. (Balt.), 1923, **58,** 337.
7. Reported at the XIth International Congress of Physiologists, Edinburgh, July, 1923. No abstract was presented because too late to be included in Proceedings.
8. Winter, L. B.: J. Physiol. (Lond.), 1923, **58,** 18.
9. Salèn, E., Acta Med. Scand. (Stockholm), 1924, **60,** 74.
10. Fuller, L. S.: J. Metab. Res. (Morristown), 1922, **1,** 609.
11. Murlin & Kramer: J. Biol. Chem. (Balt.), 1916, **27,** 481.
12. Fisher, H. F., & Noble, B. E.: Am. J. Physiol. (Balt.), 1923, **67,** 72.

BLOOD PRESSURE AND SUGAR METABOLISM

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BLOOD CONSTITUENTS IN HYPERTENSION

The facts definitely known about genuine hypertensia are few in number. It is even a problem whether this form of hypertensia represents a clinical picture. Peters, who studied the kidney function in cases of genuine hypertensia, always found symptoms of a disturbed function of the kidney. Since, however, the work of Peters has not always been confirmed, I take the genuine hypertensia as an existing clinical picture. This disease is of the greatest importance for the endocrinologist; it raises especially the two problems: (a) is there a normal sugar metabolism in hypertensia; (b) may the hypertensia be attributed to hyperfunction of the chromaffine system?

As far as I know, Neubauer (1) was the first to study sugar metabolism in cases of high blood pressure. He stated that in these cases (his patients all suffered from Bright's disease) there existed hyperglycemia. His work was confirmed by Hirsch (2), Tachau (3) and Hagelberg (4). Hitzenberger and Richter-Quittner (5) determined the blood sugar in cases of essential hypertension and found it also increased. Nevertheless, the statement that high blood pressure and high blood sugar consistently occur together has been denied repeatedly. Stilling (6), Frank (7) and Kahler (8) are among those who were not able to confirm the work of Neubauer. Riesman (9) found thyrotoxic symptoms in many patients with hypertension. He does not give reports of blood sugar estimations, but in thyroid toxicosis blood sugar generally is high.

According to Hovens Greve (10) cases of hypertension may also show hyperglycemia. This relation, according to this author, is not at all constant. Harrower (11) described symptoms of latent myxedema in hypertensia. I do not believe, however, that any other investigator agrees with this statement. Mention should be made also of an article by Fahr (12).

Hitzenberger and Richter-Quittner attribute hyperglycemia as well as hypertension to hyperadrenalinemia. Fahr, however, bases his theory on the fact, well known to all pathologists, that the blood vessels of the pancreas often suffer from sclerosis. He believes that this sclerosis causes a diminished secretion of the pancreas hormone and in this way is responsible for a hyperglycemia. Fahr also claims that there exists an antagonism between the pancreas and the adrenals. In this way a secondary hyperadrenalinemia may accompany the hyperfunction of the pancreas. Fahr's opinion is well conceived but it is based on numerous unproved statements. These quotations, though not complete, proved how little is known about the relations between blood sugar and vascular tension.

In my own studies in fifty patients with hypertension the blood sugar was measured on the empty stomach with Bang's micromethod. Thirty of these patients were tested for alimentary glycosuria with 100 gm. glucose. Ten patients took for three days a diet poor in purin substances. On the fourth day the uric acid content of the blood was determined on the empty stomach with Autenrieth's colorimeter.

	Age, Sex	Blood Pressure Riva Bocci	Blood Sugar Bang	Alimentary Glycosuria	Uric Acid mgr. /100 cc.	
1	63 m.	210-240	0.12	—	2.8	mgr.
2	41 fem.	220-250	0.19	—	1.4	
3	52 fem.	170-195	0.17	—	1.2	
4	73 fem.	200-240	0.22	—	2.4	
5	42 m.	160-220	0.09	—	2.1	
6	80 m.	145-175	0.09	—	4.1	! !
7	49 fem.	180-230	0.13	+	1.5	
8	70 fem.	180-215	0.16	—	2.0	
9*	68 fem.	170-200	0.24	—	1.4	diabetes
10	56 fem.	180-230	0.14	+	3.5	
11	63 m.	150-170	0.12	—		
12	60 fem.	135-170	0.08	—		
13	49 fem.	210-240	0.13	—		
14	59 m.	190-220	0.11	—		
15	68 fem.	155-185	0.10	—		
16	71 m.	230-265	0.12	—		
17	56 m.	230-245	0.09	—		
18	54 m.	165-180	0.10	—		
19	70 m.	265-300	0.12	—		
20	38 m.	160-210	0.14	—		
21	60 fem.	185-215	0.14	—		
22	46 m.	160-200	0.14	—		
23	68 m.	185-205	0.13	—		
24	61 fem.	210-230	0.09	+		
25	53 m.	240-270	0.15	—		
26	70 m.	140-170	0.24	—		
27	68 m.	200-225	0.17	+		
28	60 m.	175-195	0.09	—		

29	41 fem.	180-195	0.13	—
30	56 fem.	205-215	0.16	—
31	63 m.	225-235	0.20	
32	65 fem.	210-240	0.14	
33	64 m.	205-230	0.22	
34	76 m.	170-190	0.11	
35	44 fem.	200-220	0.15	
36	51 m.	230-260	0.20	
37	46 m.	205-220	0.12	
38	59 fem.	165-180	0.16	
39	70 fem.	160-195	0.10	
40	80 fem.	185-210	0.15	
41	46 fem.	230-260	0.08	
42	58 m.	150-185	0.14	
43	56 m.	200-235	0.17	
44	53 m.	210-245	0.12	
45	68 m.	160-210	0.21	
46	61 fem.	170-195	0.13	
47	64 m.	140-185	0.17	
48	42 fem.	210-245	0.18	
49	79 m.	160-175	0.23	
50	69 fem.	180-210	0.10	

*Patient 9 complained of thirst and furunculosis. She had no glycosuria; perhaps she suffered from a beginning or latent diabetes as described by Marañon.

The data of this table indicate that hyperglycemia in hypertension is exceptional, as are augmented uric acid in the blood and alimentary glycosuria.

BLOOD PRESSURE IN DIABETES

It is an important problem whether the blood pressure in diabetes is normal. The question has been raised repeatedly in medical literature. Hitzenberger (13) states that in young patients with diabetes the blood pressure is, as a rule, somewhat lower than in normal individuals of the same age. Elderly patients with diabetes have, according to this author, high blood pressure. Kylin (14, 15) on the contrary finds in young diabetics a perfectly normal blood pressure, in elderly patients a high one. According to Kylin, diabetes with hypertonia is quite another endocrine disease than diabetes with normal blood pressure. He firmly denies that in hypertonia there always is hyperglycemia, though he believes that there is an unknown relation between diabetes and hypertonia. He quotes experiments (injections of adrenalin) which sought to prove the endocrine cause of hypertonia. The problem is discussed in quite another way by Marañon (16). He often finds a high blood pressure before the detection of glycosuria. As soon as symptoms of real diabetes develop, the high blood pressure sinks. When a

person of about 40 has hypertension with, or even without, hyperglycemia he is inclined to become diabetic, especially when he suffers from adiposity. Marañon describes a pre-diabetic stage in which the patients complain of itching, neuralgia, furunculosis, etc. Rosenbloom (17) studied the blood pressure in 140 cases of diabetes. He found in ordinary uncomplicated diabetes a normal or a slightly decreased blood pressure. Hypertonia was found only when complications such as aortitis, nephritis, arterio-sclerosis or heart diseases were present. In acidosis blood pressure was generally low.

I measured the blood pressure in 161 cases of diabetes. Among these were:

A. 3 patients under 10 years.
B. 7 patients from 10-20 years.
C. 30 patients from 20-30 years.
D. 41 patients from 30-40 years.
E. 36 patients from 40-50 years.
F. 41 patients from 50-60 years.
G. 3 patients over 60 years.

A.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
7 years	Gluc., acet., diac. acid	0.23		80- 94
7 years fem.	Glucose	0.28		76-100
9 years fem.	Glucose, acetone	0.24	t. b. c. left apex	92-140

B.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
11 years fem.	Gluc., acet., diac. acid	0.22		100-125
12 years m.	Glucose, acetone	0.21		95-110
15 years fem.	Acetone, diac. acid	0.36	t. b. c. pulmonum	110-135
15 years fem.	Gluc., acet., diac. acid	0.24		90-105
17 years m.	Gluc., acet., diac. acid	0.19		85-105
18 years m.	Glucose	0.23	Br. disease, edema	130-165
18 years fem.	Gluc., acet., diac. acid	0.30		100-120

C.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
21 years m.	Gluc., acet., diac. acid	0.19		95-120
21 years m.	Glucose, acetone	0.23		90-120
21 years m.	Gluc., acet., diac. acid	0.24		85-130
23 years fem.	Glucose	0.31		100-130
23 years fem.	Glucose	0.18		110-130
23 years m.	Acetone, diac. acid.	0.20		115-140
23 years m.	Glucose	0.37		105-115
23 years fem.	Glucose	0.28		95-125
23 years m.	Gluc., acet., diac. acid	0.30	Psoriasis	80-100
23 years m.	Glucose, acetone	0.25		90-125

24 years m.	Glucose, acetone	0.20		85-100
24 years m.	Gluc., acet., diac. acid	0.34		120-135
24 years m.	Glucose	0.30	Furunculosis	120-140
24 years fem.	Glucose	0.28		100-135
24 years fem.	Glucose, acetone	0.21		80- 95
25 years m.	Glucose	0.31		110-145
26 years fem.	Gluc., acet., diac. acid	0.19	Dysenteria	105-145
26 years fem.	Glucose, acetone	0.23		85-100
26 years fem.	Gluc., acet., diac. acid	0.34		105-140
26 years fem.	Glucose	0.21		95-105
26 years fem.	Glucose	0.28	Ulcus ventriculi	100-120
26 years fem.	Glucose	0.34		100-145
26 years fem.	Gluc., acet., diac. acid	0.30	Ulcus ventriculi	90-105
26 years m.	Acetone, diac. acid	0.21		80-100
28 years m.	Acetone, diac. acid	0.18		95-110
28 years m.	Gluc., acet., diac. acid	0.26		120-145
28 years m.	Glucose	0.31		115-125
30 years m.	Glucose.	0.34	t. b. c. pulmonum	80-115
30 years m.	Acetone, diac. acid	0.46		100-125
30 years fem.	Glucose	0.20	t. b. c. pulmonum	95-135

D.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
31 years fem.	Glucose	0.30		90-140
31 years fem.	Glucose	0.21	t. b. c. pulmonum	120-135
31 years fem.	Gluc., acet., diac. acid	0.36		85-120
31 years fem.	Acetone	0.19		90-110
31 years m.	Glucose, acetone	0.32	Ulcus ventriculi	115-140
32 years fem.	Glucose, acetone	0.27		100-135
32 years fem.	Gluc., acet., diac. acid	0.40		80-120
32 years m.	Glucose	0.23		120-145
32 years m.	Glucose	0.21	Ulcus duodeni	75-100
32 years fem.	Gluc., acet., diac. acid	0.25		105-120
32 years fem.	Acetone	0.14		140-165
32 years m.	Acetone, diac. acid	0.12		105-130
32 years fem.	Acetone	0.19		95-140
32 years fem.	Glucose	0.31		85-125
32 years m.	Glucose	0.24		70-100
32 years m.	Glucose	0.30	Syphilis III	95-110
32 years m.	Gluc., acet., diac. acid	0.25		105-120
33 years fem.	Glucose, acetone	0.29		95-130
33 years fem.	Acetone	0.20		110-140
34 years m.	Glucose	0.27	Psoriasis	95-110
34 years fem.	Glucose	0.26		90-125
34 years fem.	Acetone, diac. acid	0.19		75-110
34 years fem.	Gluc., acet., diac. acid	0.24		120-160
34 years fem.	Glucose	0.30		85-110
34 years m.	Acetone	0.20		100-125
34 years fem.	Glucose	0.40		100-110
34 years m.	Glucose	0.39		85-100
35 years fem.	Glucose	0.32	Ulcus ventriculi	90-130
36 years m.	Acetone	0.09		80-100
37 years fem.	Acetone, diac. acid	0.12		105-140
37 years m.	Gluc., acet., diac. acid	0.19		1[illegible]140
37 years m.	Glucose, acetone	0.26		8[illegible]140
37 years m.	Glucose	0.29		90-110
37 years m.	Acetone, diac. acid	0.18		75-100
38 years m.	Acetone, diac. acid	0.26		120-145
38 years fem.	Gluc., acet., diac. acid	0.33	Caries vertebrae	80-110

38 years m.	Glucose	0.28		95-120
38 years fem.	Acetone	0.19		100-135
38 years fem.	Acetone, diac. acid	0.21		105-140
39 years fem.	Gluc., acet., diac. acid	0.43	Cardiospasm	90-120
40 years fem.	Gluc., acet., diac. acid	0.35		125-140

E.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
42 years m.	Acetone	0.22		120-165
42 years m.	Glucose, acetone	0.26		140-180
42 years m.	Glucose	0.30		130-165
42 years fem.	Glucose	0.24	Menopause	95-140
42 years fem.	Glucose	0.21		160-200
42 years fem.	Gluc., acet., diac. acid	0.29	t. b. c. pulmonum	85-140
42 years m.	Acetone	0.19	Insuf. mitralis	95-120
43 years m.	Glucose	0.20		160-200
44 years m.	Glucose	0.23		120-145
44 years fem.	Glucose	0.31		130-160
44 years fem.	Glucose, acetone	0.30		95-140
44 years fem.	Glucose	0.27	Nephritis chronica	220-265
44 years fem.	Acetone, diac. acid	0.20		160-185
45 years fem.	Glucose	0.30		140-160
46 years m.	Gluc., acet., diac. acid	0.36		155-185
46 years m.	Glucose	0.24		170-205
46 years m.	Glucose	0.27		165-190
46 years fem.	Glucose	0.21	Menopause	110-140
46 years fem.	Glucose	0.35		105-145
46 years fem.	Glucose	0.21		170-205
47 years m.	Glucose, acetone	0.33	Ulcus ventriculi	105-140
47 years fem.	Acetone, diac. acid	0.40	Graves' disease	170-220
47 years m.	Glucose, acetone	0.22		180-210
48 years m.	Glucose, acetone	0.28		155-185
48 years m.	Glucose	0.24		195-240
48 years m.	Glucose	0.30		160-185
48 years m.	Glucose	0.33		150-165
49 years m.	Gluc., acet., diac. acid	0.21		190-205
49 years fem.	Glucose	0.19		170-215
50 years m.	Glucose	0.17		160-200
50 years m.	Diacetic acid	0.24	t. b. c. pulmonum	90-135
50 years fem.	Glucose	0.21		160-210
50 years fem.	Acetone, diac. acid	0.14		200-235
50 years fem.	Glucose, acetone	0.25		160-205
50 years fem.	Glucose	0.28	Cholelithiasis	100-135
50 years m.	Glucose	0.34		190-235

F.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
52 years m.	Glucose	0.30		160-185
52 years m.	Glucose	0.21	Ulcus ventriculi	170-185
52 years m.	Glucose	0.26		140-180
52 years m.	Glucose	0.24		110-165
52 years fem.	Glucose, acetone	0.19		190-215
52 years fem.	Glucose	0.18		145-170
52 years fem.	Acetone	0.14	Emphysema-pulm.	185-205
52 years fem.	Gluc., acet., diac. acid	0.35		160-190
53 years m.	Glucose	0.26		155-180
53 years fem.	Glucose	0.24		100-145
53 years fem.	Glucose, acetone	0.31	Cholelithiasis	170-240
54 years fem.	Glucose	0.24		145-160

55 years m.	Glucose, acetone	0.31		140-170
55 years m.	Acetone	0.20		105-120
56 years m.	Acetone, diac. acid	0.20		95-140
56 years m.	Glucose	0.31	Bright's disease	230-255
56 years fem.	Glucose	0.28		160-195
56 years fem.	Glucose	0.25		110-135
56 years m.	Glucose	0.30		135-170
56 years m.	Glucose	0.29		105-125
56 years m.	Acetone	0.19		140-170
56 years m.	Gluc., acet., diac. acid	0.23	Ulcus duodeni	130-170
56 years m.	Glucose	0.18		100-125
56 years m.	Glucose, acetone	0.23		110-155
56 years m.	Glucose	0.26		105-140
56 years fem.	Glucose	0.38	Bright's disease	270-295
56 years fem.	Glucose	0.22		180-195
56 years fem.	Acetone	0.20		140-165
56 years m.	Glucose	0.29		110-135
58 years fem.	Glucose	0.34		145-170
58 years fem.	Glucose	0.37	Bright's disease	200-235
59 years m.	Glucose	0.28		160-185
59 years m.	Acetone	0.12		195-215
59 years m.	Glucose, acetone	0.29		135-160
60 years fem.	Glucose, acetone	0.40	Bright's disease	190-240
60 years fem.	Glucose	0.26		140-180
60 years m.	Acetone	0.13		160-195
60 years m.	Glucose	0.28	Ulcus ventriculi	155-180
60 years m.	Glucose	0.27		140-175
60 years m.	Acetone	0.20		205-230
60 years fem.	Gluc., acet., diac. acid	0.35	Carcinoma recti	95-120

G.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
68 years fem.	Glucose	0.23	Arteriosclerosis	220-245
72 years fem.	Glucose	0.21	Arteriosclerosis	230-270
74 years fem.	Glucose	0.24	Arteriosclerosis	190-225

Conclusion:

In young diabetics blood pressure is normal; in older patients with diabetes, hypertension is the rule. No relation between complication and blood pressure was found (except, of course, Bright's disease and arterio-sclerosis). Acidosis does not cause a diminished blood pressure.

BIBLIOGRAPHY

1. Neubauer: Biochem. Ztschr. (Berl.), 1910, **25**, 284.
2. Hirsch: Biochem. Ztschr. (Berl.), 1916, **75**, 189.
3. Tachau: Deutsches Arch. f. klin. Med. (Leipz.), 1911, **102**, 597.
4. Hagelberg: Berl. klin. Wchnschr., 1912, **50**, 40
5. Hitzenberg & Richter-Quittner: Wien. Arch. f. innere Med., 1921, **2**, 189.
6. Stilling: Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1911, **66**, 238.
7. Frank: Deutsches Arch. f. klin. Med. (Leipz.), 1911, **103**, 397.
8. Kahler: Wien. Arch. f. innere Med., 1922, **4**, 129.
9. Riesman: J. Am. M. Ass. (Chicago), 1919, **73**, 330.
10. Hovens Greve: Inaug. Diss. (Leyden), 1919.
11. Harrower: Med. Rec. (N. Y.), 1920, **98**, 854.
12. Fahr: Berl. klin. Wchnschr., 1921, **56**, 730.
13. Hitzenberger: Wien. Arch. f. innere Med., 1921, **2**, 461.
14. Kylin: Zentralbl. f. innere Med. (Leipz.), 1921, **45**, 873.
15. Kylin: Zentralbl. f. innere Med. (Leipz.), 1922, **46**, 329.
16. Marañon: Zentralbl. f. innere Med. (Leipz.), 1922, **46**, 169.
17. Rosenbloom: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1921, **18**, 236.

PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF GOITER.

Bloomington, Ill., January 23, 24, 25, 1924.

Edited by J. D. MOSCHELLE

FIRST ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

The first session convened at St. Joseph's Hospital, 7:45 a. m., January 23.

The program committee announced that they felt justified in featuring ethylene anaesthesia at this annual meeting in view of the fact that it is attracting great interest at the present time and it was so satisfactory at the preliminary clinic held December 17.

OPERATIVE CLINIC: Held by Dr. E. P. Sloan, assisted by Drs. G. A. Sloan, Herman Wellmerling, J. D. Moschelle, and Geo. Newell. Four patients were operated under nitrous oxide oxygen anaesthesia, administered by Dr. Wm. Young. Four patients were operated upon under ethylene oxygen anaesthesia, administered by Dr. Dennis Rupp, assisted by Mr. P. J. McCurdy of the Safety Oxygen Gas Machine Company. The anaesthesia was featured and comparison of effects of nitrous oxide and ethylene was made. It was obvious that ethylene is more potent than nitrous oxide, that the patients are anaesthetised quicker and recover normal consciousness sooner than after nitrous oxide.

At 11:30 it was announced by the secretary that 215 had registered, and all were urged to join the Society. A recess was taken for lunch.

AFTERNOON SESSION

At Mennonite Hospital. Operative Clinic: Dr. E. P. Sloan. Four patients were operated on under ethylene. Very satisfactory ethylene anaesthesia.

At 3:30 adjourned to St. Joseph's Hospital, where arrangements had been made for Dr. Andre Crotti of Columbus, Ohio, to hold an operative clinic.

Dr. Crotti operated two patients with large nodular colloid goiters. All present were invited as guests of the Sloan Clinic, to a smoker to be held at the Illinois Hotel at 9:00 p. m.

Wednesday and Thursday the following program was carried out:

JANUARY 24, 1924—MORNING—7:00 A. M.

The meeting was called to order by Dr. E. P. Sloan, president, who introduced the vice-president, Dr. Geo. W. Newell, of Burlington, Wisconsin, and requested him to take the chair and act as presiding officer during the session.

The vice-president introduced Dr. Harlan Hart of Bloomington, Illinois.

Dr. Andre Crotti of Columbus, Ohio, was then introduced and he held a diagnostic clinic. He discussed non-toxic and toxic parenchymatous goiters, non-toxic and toxic diffuse colloid goiters, and non-toxic and toxic nodular colloid goiters, and illustrated each kind with several patients.

Dr. J. L. DeCourcy of Cincinnati, Ohio, was introduced and heard on *"Surgery of the Thyroid."*

Dr. E. G. Blair of Kansas City, Missouri, discussed *"Secondary Goiter Operations."* He also reported conclusions from a large series of cases and showed two patients and discussed them.

Dr. Wm. Englebach of St. Louis, Missouri, then conducted a diagnostic clinic on endocrinology, illustrated with lantern slides.

The meeting adjourned at 12:30.

AFTERNOON, 1:30 O'CLOCK

The afternoon meeting was called to order by the vice-president, Dr. Geo. W. Newell, who introduced Dr. Crotti of Columbus, Ohio. Dr. Crotti gave an address on *"The Etiology of Endemic Goiter and Toxic Goiter."*

Dr. Wayne Babcock of Philadelphia, Pennsylvania.

Address: Dr. E. R. Arn, Dayton, Ohio. *"An Analysis of Types of Goiter with Indications for Treatment."*

Address: Dr. F. N. Wilson, Ann Arbor, Michigan. *"Cardiac Disturbances in Association with Diseases of the Thyroid Gland."*

Dr. E. P. Sloan: I want you to see and hear a few words from a man who has accomplished much for scientific medicine. Especially should we in the Middle West be grateful to him. He is the father and mother and also the wet nurse of the great

Tri-State District Medical Association, the association that has had most wonderful four-day programs annually for several years. All honor to the managing-director who has been so largely instrumental in its success. I want to call upon Dr. William B. Peck of Freeport, Illinois.

Dr. William B. Peck, Freeport, Illinois: I believe you are pursuing the right course in the study of goiter. The medical treatment of goiter is apparently making wonderful prograss with the careful and judicial use of iodine and other medical treatment. I was in the Kocher Clinic in Berne, Switzerland, when practically every case of goiter was treated by surgical technique and treatment. Today, I understand that 50 per cent of the cases that were formerly treated surgically are now being treated medically. Dr. Sloan has asked me to say a word about the Tri-State Medical Association.

The next annual assembly will be held at Milwaukee, Wisconsin, October 27th, 28th, 29th and 30th. We expect next year to supervise a clinic tour to Canada, British Isles and Paris with side trips to other clinical centers. The tour is supposed to start on the 16th of May, 1925. Clinics in Toronto, Montreal, Liverpool, London, Leeds, Edinburgh, Glasgow, Newcastle-on-the-Tyne, Dublin and Paris will be arranged in advance. These clinics will be conducted by the most eminent members of the profession in these cities. The cost of the trip, including everything except board in Canada and lasting in the neighborhood of seven weeks, will be approximately $795.00. The reservations are fast filling up, and we would advise the physicians who wish to go to notify us as early as possible.

Address: Dr. Horace M. Brown, Milwaukee, Wisconsin. *"The Biologic Causes of Incompetency."*

Address: Dr. Arnold Jackson, Madison, Wisconsin. *"The Relation of Basal Metabolic Rate to Diseases of the Thyroid Gland."*

Address: Dr. F. M. Hagans, Lincoln, Illinois. *"Radium Treatment of Goiter."*

Banquet at the Illinois Hotel at 7:00 p. m. Dr. E. C. Williams, president McLean County Medical Society, presiding. Dr. Horace M. Brown, Milwaukee, Wisconsin, acted as toastmaster. Dr. L. C. Taylor, president of the Illinois State Medical Society; Dr. I. D. Rawlings, director of Illinois State Board of Health; Dr. W. B. Hight, Des Moines, Iowa; Dr. E. W. Rowe, Lincoln, Nebraska; Dr. Andre Crotti, Columbus, Ohio; Dr. W. B. Peck, manager Tri-State Association; Dr. H. S. Plummer, Rochester, Minnesota; Dr. Wm. Engelbach, St. Louis, Missouri; Dr. Arnold Jackson, Madison, Wisconsin; Dr. Wayne Babcock, Philadelphia, Pennsylvania; Dr. W. T. Scott, Temple, Texas; Dr. E. C. Blair, Kansas City, Missouri; Dr. Wm. King,

Seattle, Washington; Dr. J. L. DeCourcy, Cincinnati, Ohio, responded to toasts. Eighty-eight were in attendance.

JANUARY 25, 1924—MORNING—8:00 O'CLOCK

The meeting was called to order by Dr. Newell.

Address: Dr. Roswell Pettitt, Ottawa, Illinois. *"Incipient Goiter vs. Incipient Tuberculosis."*

Address: Dr. E. W. Rowe, Lincoln, Nebraska. *"The Roentgen Treatment of Thyrotoxicosis."*

This paper was followed by discussions by several X-ray and radium men who were present: Dr. Cantrell and Dr. Grote of Bloomington; Dr. Jackson of Madison, Wisconsin; Dr. Goodman and Dr. McGee of Peoria; Dr. Gillette of Toledo, Ohio.

Dr. Wayne Babcock of Philadelphia, Pennsylvania, conducted a diagnostic clinic. This clinic was followed by discussions by Dr. Jackson of Madison, Wisconsin; Dr. Arn of Dayton, Ohio; Dr. Dryer of Aurora, Illinois, and Dr. Moschelle of Indianapolis, Indiana.

Dr. J. W. Turrentine of Washington, D. C., was unable to be present. His paper on *"Use of Seaweed in the Prevention and Treatment of Goiter,"* was read by Dr. Moschelle, the secretary.

Dr. Frank H. Lahey of Boston, Massachusetts, was unable to be present. His paper, *"A Review of Another Year's Work with Thyroid Diseases,"* was read by Dr. Sloan.

It was suggested to the chair that Dr. Kennan Dunham of Cincinnati, Ohio, be on the program at the Chicago meeting, the Tuesday before the A. M. A. meeting.

Dr. Moschelle asked the members to send in questions and answers about perplexing problems so that they may be brought up at the Chicago meeting.

The meeting then adjourned to St. Joseph's Hospital, where lunch was served and Dr. Sloan held an operative clinic. Six thyroidectomies were done.

The following officers were elected for the ensuing year:

President.....E. P. Sloan, Bloomington, Ill.
Vice-President.....George W. Newell, Burlington, Wis.
Secretary.....J. D. Moschelle, Indianapolis, Ind.
Treasurer.....J. R. Young, Terre Haute, Ind.

Councillors

Dr. Wayne Babcock.....Philadelphia, Pa.
Dr. E. W. Rowe.....Lincoln, Neb.
Dr. E. R. Arn.....Dayton, Ohio
Dr. R. H. Stevens.....Sioux Falls, S. D.

Dr. R. A. McGillicuddy.....Turner's Falls, Mass.
Dr. F. S. Wetherell.....Syracuse, N. Y.
Dr. F. B. Dorsey, Jr.....Keokuk, Iowa
Dr. G. S. Fahrni.....Winnipeg, Canada
Dr. L. W. Frank.....Louisville, Ky.
Dr. A. C. Scott, Jr.....Temple, Texas
Dr. N. W. Gillette.....Toledo, Ohio
Dr. Joy.....Calumet, Mich.
Dr. B. T. King.....Seattle, Wash.

A one-day meeting with a banquet in the evening will be held in Chicago, Tuesday, June 10, at the Hotel Sherman.

PRELIMINARY CLINIC

December 17, 1923. Demonstration of Ethylene Gas given for the American Association for the Study of Goiter, at the Sloan Clinic, Bloomington, Illinois.

CASE ONE.

Female: Goiter non toxic. Preliminary hypodermic. Morphin ¼. Atropin 1/150. Patient took anaesthetic without resistance and was completely anaesthetized in 1½ minutes. Good relaxation, no change in color, pulse, blood pressure or respiration during the entire operation. Complete consciousness returned within two minutes after the anaesthetic was discontinued.

CASE TWO.

Female: Goiter severely toxic. No preliminary hypodermic. Complete anaesthesia in three minutes. No cyanosis, no change in pulse, respiration or blood pressure during the operation. Regained complete consciousness within two minutes after the anaesthetic was discontinued. Complained of considerable burning from operation wound.

CASE THREE.

Female: Carcinoma of the pylorus. Preliminary hypodermic. Morphin ⅙. Atropin 1/150. Complete anaesthesia in two minutes. Complete relaxation. No cyanosis or change in respiration, blood pressure, or pulse rate during the entire operation. Returned to complete consciousness in three minutes. No post-operative vomiting.

CASE FOUR.

Strong muscular man 28 years of age, doing hard manual labor. Sub-acute perforation of a duodenal ulcer. No preliminary hypodermic. Complete anaesthesia in four minutes. Perfect relaxation. Cholecystectomy and gastro-enterostomy were performed. Incision closed by shoe string suture in each layer of fascia. In drawing the shoe string suture the abdominal wall raised high above the intestines. This could not occur unless complete relaxation was present.

No change in pulse, respiration, color or blood pressure during the entire administration of Ethylene. Patient returned to complete consciousness in three minutes after anaesthetic was discontinued. No post-operative vomiting.

(Blood pressures were taken on these patients that afternoon and again that evening with practically no change in findings. None vomited after operation.)

CASE FIVE.

Large goiter with pressure symptoms. No preliminary hypodermic. Complete anaesthesia in three minutes. No change in pulse rate, respiration or color during the administration. Returned to complete consciousness within three minutes after anaesthetic was discontinued. No post-operative vomiting.

CASE SIX.

Colloid goiter, non-toxic. Preliminary hypodermic, Hyoscin 1/200, Morphin ¼. Anaesthetised in two minutes with Ethylene. Complete relaxation. No change in pulse rate, respiration, or color of blood. After ten minutes Ethylene was discontinued and Nitrous-Oxide started on the same machine. It required more than double the volume of Nitrous-Oxide than it had required of Ethylene to keep the patient anaesthetised. Blood was darker but no cyanosis. No change in pulse, or respiration during the entire operation. No post-operative vomiting.

CONCLUSIONS

The advantages of Ethylene over Nitrous Oxide are:

It is a more effective and powerful anaesthetic.

It can be used without a preliminary hypodermic to much better advantage.

Its odor is not offensive after the first inhalation or two.

It is quicker in action.

It is cheaper because less is required to keep the patient anaesthetised.

Its known disadvantages are:

Its inflammability.

Its slight odor.

It was decided to feature Ethylene Anaesthetic at the annual meeting in January.

OPERATIVE CLINIC NOTES

First session convened at St. Joseph's Hospital, Bloomington, Illinois, 7:45 a. m., January 23, 1924.

The meeting was turned over to the Program Committee.

It announced that the first operative clinic would begin in the large operative room at 8:00 a. m.

OPERATIVE CLINIC

DR. E. P. SLOAN:

The first patient is a doctor's daughter, aged 19 years. She has been in poor health for about five years. Until two years ago she complained of little except nervousness. Since that time she has had marked cardiac disturbances with tachycardia on slight exertion. She is hyper-sensitive to heat and says that she "Has restlessness without reason for it." Her basal metabolism rate is plus 30. Her pulse rate 96 to 130. Her systolic blood pressure is 135.

On examination we find small thyroid with one well marked palpable nodule in the right lobe. We believe that her nervousness, restlessness and the changes in the vessel of the retina are all due to endocarditis and a similar condition affecting the blood vessels of her entire circulatory system.

In this case we will make a small incision 1½ inches long. Then we raise the flap, and separate the muscles by blunt dissection. Direct inspection shows that the gland has been rotated on the trachea to the right. That the trachea itself is rotated to the right. This adenoma about as large as the end of your thumb that was apparently in the lower portion of the right lobe is the isthmus. We will now separate its superior border from the trachea.

I wish you now to observe how the gland is mobilized. Since the trachea is released from the superior border of the isthmus it has rotated to the left back to its normal position. By dislocating the right lobe and bringing it forward we see that the right lobe has a normal appearance except its anterior third. The anterior third is hard and has a granular feel, typical of hyperplasia. By removing this anterior third we have left about two-thirds of the right lobe which is apparently normal. There is enough hyperplastic tissue in this portion that we have removed to account for all the symptoms in this case. Having removed this with the isthmus, and tied the blood vessels, we now dislocate the left lobe and bring it forward. Here on the posterior border of the left lobe we find a small solid adenoma. This we remove and now you see that the remains of this left lobe fold together into quite a normal shaped left lobe, although quite small. It looks like this was the original offender. It has the appearance of what is usually termed a foetal adenoma. It certainly has been present from birth or from early childhood.

Our diagnosis from conditions found at operation is toxic adenoma in the posterior border of the left lobe, with a later development of hyperplasia in the right lobe and isthmus. We will close the incision with two linear silkworn gut sutures, passed back and forth from side to side, from the outer angle of the incision, drawing the ligature back and forth subcutaneous fascia are brought together.

A running suture of catgut can be used for this, but so frequently catgut knots do not absorb in this situation that the silk worm is preferable. This fascia should be held together for ten days. If it is released earlier the fascia union is not solid and the scar will spread later, sometimes even after two to four years leaving a wide scar that is quite unsightly. The skin edge can be brought together with clips, adhesive strips, equisetine, dermol suture, or horse hair. Fine equisetine can be left in place three days without danger of scar. Dermol suture four days and horse hair can be left six days. The only objection to horse hair is that it is rather hard to handle, it takes longer time to sew the skin.

DR. WM. YOUNG (Anaesthetist.)

This patient is getting Nitrous Oxide Oxygen anaesthesia. This has been the regular anaesthetic in use here for several years. This patient received, three minutes before she was brought up, a preliminary hypodermic of Morphin one-sixth and Atropin 1/200. We took eight minutes to completely anaesthetise her. We rarely keep them in the analgaesic stage. We have them entirely asleep although not thoroughly relaxed. By pushing the gas a little bit harder we could thoroughly relax her but it is not necessary for goiter work. In abdominal work, and all of the abdominal work here is done with gas anaesthesia, we have them relaxed. I want you to notice that this patient has not been blue or cyanotic at any time. She has not moved and there is no change in color, pulse, or respiration.

While they are closing up the skin we will cut off the gas and continue with the same amount of oxygen as before. The last stitch has been made we will remove the mask. She is moving and has opened her eyes within less than one minute after the mask was removed.

DR. E. P. SLOAN:

This next case, Mrs. P. S., age 19, lives here in Bloomington. She came in with intense nervousness, irritability of the heart, fine tremor and was markedly toxic. Her basal metabolism rate was plus 48, her pulse was 146, her systolic blood pressure was 126, her dyastolic was only 66. She complained of choking and swallowing sensations which could not be due to the size of the gland. She had her tonsils and adenoids removed 12 years ago, at the age of seven. The uncomfortable sensation in her throat began shortly afterward. She states that at the age of twelve her goiter was plainly visible and that it hurt her to touch it. At about the same time she began to complain of palpitation, shortness of breath and nervousness. In our opinion this patient is a typical case of strumitis and inflammation of thyroid, secondary to throat infection. This chronic inflammation of the thyroid has doubtless been present for 12 years and sclerotic changes and hyperplastic degeneration have occurred. As you see, she is not exophthalmic to an appreciable degree. She has, however, a marked endocarditis and from the history we feel certain that this

endocarditis has been present for ten years. Therefore, we assume myocardial changes have occurred. As she is only 19 we are quite confident that removal of the degenerated portion of the gland will be of marked benefit. Our definition of goiter is: *Goiter is the diseased portion of the thyroid gland.*

We will now remove the gland by technique similar to that of the previous case. You will notice upon exposure of the gland that there is a very long pyramidal lobe that extends up above the cricoid cartilage, which we will release from the trachea, as the first step in our operation. Patients with this long pyramidal tract are apparently much more likely to develop secondary Strumitis from throat infection than those without it. In fact, I do not remember of ever having seen a case of strumitis secondary to a throat infection when the isthmus was small and no pyramidal projection present.

Having mobilized the gland, we now examine both sides. I am sure that you can see from where you are sitting that the Anterior or inner portion of both lateral lobes look granular. You can see along the outer side of each lobe the line of demarcation between the diseased portion of the gland and that which is yet comparatively normal. We have now resected both lobes and have left the Posterior third portion of each lobe. The portion remaining is normal to touch and its blood supply has not been interfered with. We will close the same as the previous case.

DR. DENNIS RUPP, Anaesthetist:

This patient had one-eighth grain of Morphin, hypodermically, 30 minutes before the anaesthesia was started. The incision was made 3½ minutes after the anaesthesia began. You have seen that there has been no change in respiration or color. There has been no change in pulse rate or blood pressure. She is moving and has opened her eyes in less than one minute from the time the Ethylene was stopped.

It is just two minutes now since we stopped the Ethylene, and you will observe that she is practically normal, so far as consciousness and mental equilibrium is concerned. This is one of the most gratifying features of Ethylene. The patients not only come out much quicker than from under Nitrous Oxide, but they come entirely out, and are entirely conscious. She is not perspiring.

DR. E. P. SLOAN:

This third case, Mrs. J. H., Peoria, Illinois, age 24, states that a tumor was noticeable in the right lobe since 10 years of age. It became hard, somewhat painful, with discomfort upon swallowing six months ago, following a mild throat infection. Intense nervousness with marked tremor, palpitation of the heart and shortness of breath soon developed. During the last three months she has complained of choking spells when lying down. These choking spells are asthmatic in character, accompanied by palpitation of the heart and great restlessness. The gland is not very prominent but is quite hard and has

the peculiar feel on palpation that is characteristic of acute strumitis. Our diagnosis is acute strumitis following a throat infection. We do not think that the old tumor, which is doubtless a foetal adenoma, has anything to do with the toxic condition that is present. She has, of course, a marked endocarditis which is responsible for the tachycardia, and shortness of breath. Her basal metabolism rate was plus 68 when she came in and after five days preparation it was down to 44, with a pulse rate of 97.

We expose the gland in the same manner as the previous operations. You can now see the prominent pyramidal lobe, which extends up above the cricoid cartilage. This is another case of strumitis with a prominent pyramidal lobe. Apparently throat infections are prone to extend down into the thyroid when this lobe is present. This is merely an observation and I merely call your attention to it. We now separate this pyramidal lobe from the trachea as the first step in the procedure. By extending the dissection of the anterior capsule out toward the upper poles, we release the upper poles from the perilaryngeal structures.

The gland is now mobilized so that we move it up and down on the trachea over a distance of more than one inch before we encounter any resistance. We will now rotate the right lobe to the inner side and ligate the upper pole with No. 1 plain catgut. We will drop the lobe back and start in at the lower pole and flex the lobe upon itself, rotate inward, sever the lower pole and as the gland is released we get flexion, rotation and extention out through our incision and this brings all of its attachments successively into view, so that they are easily clamped and cut, and by cutting the upper poles near the ligature previously applied this lobe is delivered entirely without any tension, or rotation of the trachae. We now resect the anterior half of the left lobe in practically the same manner.

If the tumor were very large it would be very difficult through a small incision and without cutting the muscles to get to the superior pole, so we would wait to ligate the superior thyroid vessels until after the superior attachments of the isthmus and the pyramidal lobe, the attachments of the inner side of the superior pole to the perilaryngeal structures and of the thyroid to the trachea which are at about the junction of the isthmus to the lateral lobe, are severed, the lobe flexed, rotated, and the inferior pole and the attachments between the lower border of the isthmus and the trachea severed, the lobe delivered and its attachments severed in rotation from the inferior pole to the superior pole, leaving a pedicle at the superior pole containing merely the branches of the superiod thyroid. Then we would ligate this pedicle and release the lobe. In other conditions by remembering and observing the same mechanical principles that the Obstetrician has in mind in a vertex presentation, it is easy to deliver any size tumor through a small opening without cutting any muscle fibers and without disturbing the respiration by traction, twisting, or pressure

upon the trachea. In our early experience we sometimes had a collapse of the trachea with great embarrassment of the respiration. In several cases so severe that we had to pass an open-ended catheter down through the trachea beyond the point of obstruction to save the patient's life, even though we had cut the muscles transversely clear out to the edge of the sterno cleido-mastoid. Since we have observed the mechanical principles that are commonly observed in obstetrics, we have not had a single collapse of the trachea and have not yet cut the muscles in over 3000 operations. Observance of the mechanical principles have made the operation an easy one in all cases when without observance of these principles it is sometimes a very difficult one.

DR. WILLIAM YOUNG, Anaesthetist:

This patient had a preliminary hypodermic of ¼ grain of Morphin and 1/200 grain of Hyoscin forty minutes before the anaesthetic was begun. She was very sleepy from the effect of the hypodermic and her respiration was apparently affected, therefore, she was anaesthetised very quickly. The incision was made in three minutes after the anaesthetic was begun. She was given 1/40 of a grain of strychnia ten minutes after the anaesthetic was begun. Strychnia is apparently a stimulant to the respiration and seems to have a very prompt and dependable effect when the respiration is affected by Hyoscin. Within ten minutes after she received the strychnia her respiration became deeper. She required less oxygen to keep her pink and her condition has been perfectly satisfactory ever since. It requires a very small amount of gas to keep her anaesthetised.

It is just three minutes since the mask was removed from her face. She is conscious and speaking. She has made all of the vowel sounds with good, clear voice tone.

DR. E. P. SLOAN:

This fourth case, Mrs. G. H. Lincoln, Illinois, age 20. She states that she has had a goiter for 7 years, but it never gave her any trouble until about two years ago. She had recurrent attacks of tonsilitis, and developed rheumatism. Her tonsils were removed two years ago and about that time she became very nervous.. Typical tremors, palpitation of the heart, shortness of breath, tenderness and sense of discomfort of her thyroid. Her pulse rate has been about 120 for the last two years. She is restless without a cause. She does not sleep well the latter part of the night, and she gives out easily. Tuberculosis has been suspected, but her temperature curve has not been consistent with her pulse rate. Exercise or excitement will increase her pulse rate but does not increase her temperature. This is a typical case of recurrent strumitis, secondary to throat infections. It has been markedly aggravated during the last year by pregnancy. Her child is nine months of age and her symptoms have been severe since its birth.

The fluoroscopic and physical examinations show her heart to be markedly enlarged. She undoubtedly had some dilatation of the heart at the time her child was born. Of course she has had endocarditis ever since the strumitis developed. The question for thought is whether iodine treatment or any other form of preventive measures would have prevented this patient from developing strumitis. If her tonsils had been removed before the infection extended from them down to the thyroid the strumitis would doubtless not have developed. Of course she would have had her simple goiter, which is a well defined tumor in the right lobe of her thyroid, but the disturbance of the heart, the tremor, the restlessness, the increased size and tenderness of the gland would not have occurred. If any form of preventive treatment would have prevented the infection of this gland and the changes that have occurred from the infection, why not depend upon the same preventive treatment for the prevention of tonsillar infection. I cannot see why it is possible to prevent infection of the thyroid by internal medication when it is not possible to prevent infection of the tonsils.

It is just two minutes since the Ethylene anaesthetic was begun. You notice that relaxation is complete. You will also notice how pink the blood is. The blood is apparently a lighter pink during the administration of Ethylene than normal. With Nitrous-Oxide there is a slightly bluish tint to the blood which in our opinion is not cyanosis but is due to the color of the Nitrous-Oxide in the blood. Ethylene appears to have the effect of making the blood a lighter pink than normal from the same reason.

We find as we expected a high long pyramidal lobe. You can see from where you are sitting this hard adenoma, about the size of a walnut with the hull on, in this right lobe. It is not the cause, however, of the hard slightly nodular areas, chain like to the touch that extends through the anterior portions of both lobes and the isthmus. I am sure that from where you are sitting you can see the line of demarcation between the portions of the thyroid that have undergone change and these posterior portions which are apparently normal. We will not ligate the superior poles because we want to leave the blood supply to the portions that are left intact.

We have now removed by the same technique as the previous cases the anterior two-thirds of the lobes and the isthmus with the pyramidal lobe.

DR. DENNIS RUPP, Anaesthetist:

This patient had no preliminary hypodermic but was given ⅙ grain of Morphin hypodermically twenty minutes ago to make her comfortable immediately following the operation. Her pulse, respiration and blood pressure have not changed. She has not been cyanotic, and has been perfectly relaxed.

She repeated the vowel sounds after me one minute after the mask was removed and is now perfectly conscious. Her consciousness

has completely returned. When a patient comes out from Ethylene anaesthetic they come completely out and do not have a border line stage like they do after most anaesthetics. All of her mental faculties are apparently perfectly normal.

DR. E. P. SLOAN:

This fifth case, Mrs. A. S., Gibson City, Illinois, age 26, has had a large goiter ever since she can remember. Ten years ago it was soft and smooth, but caused her no trouble. Her symptoms have developed gradually. She has slight tremor, pulse of 100, blood pressures: systolic 112, dyastolic 76, basal metabolism, minus 10. The gland at this time is large and nodular, not tender, no discomfort upon swallowing. She has a large nodular colloid. So much of the gland is not functioning that she has less thyroid secretion than normal. We are quite certain that after the diseased or abnormal portion of her gland is removed that her basal metabolism rate will return to nearer normal. Why this happens we do not know.

We will now expose the gland. You will observe that there is practically no middle lobe, a very small isthmus. We will remove it by the regular Sloan Technique. It is impossible to get to the superior thyroid vessels with this small incision without cutting the muscle fibers with the gland in place, so we will remove the right lobe in the regular manner. Flexion, rotation, and extention enables us to sever the attachments consecutively and deliver the lobe until we have only the superior vessels that are not severed. By retraction upward with a narrow retractor we are able to ligate these blood vessels above the upper pole. Severing them, releases the right lobe completely. As we have removed the right lobe completely, we will try to find some normal tissue in the left lobe that can be left. We now have the left lobe delivered out through the incision and you can plainly see the line of demarcation between the portion of gland that has undergone the colloid degeneration and this narrow layer on the posterior inner surface. This layer is apparently only about ¼-inch thick but extends fully ½ of the way around the large tumor. We have now removed the tumor mass from the left lobe and this narrow layer falls together in such a manner that we have quite a normal looking left lobe.

DR. WILLIAM YOUNG, Anaesthetist:

This patient had ⅙ grain of Morphin, 1/200 grain Hyoscin 30 minutes before the anaesthetic was begun. She has gone through the operation in fine shape with no cyanosis and no changes in pulse, respiration or blood pressure. She repeated the vowel sounds in four minutes after the anaesthetic was discontinued.

DR. E. P. SLOAN:

This sixth case, Mrs. F., Gibson City, age 27, says she has had a goiter since she was 12 years of age. She has definite tremor of the tongue, a fine rapid tremor of the fingers with palpitation of

she came in, but after a night's rest was only 104. Her systolic blood pressure 118, her dyastolic 62, her basal metabolism rate is minus 14, her hemoglobin is down to 70. She has two children, 7 and 5 years of age, respectively, and states that since the birth of her last child she has gradually run down, that she cannot stand as much as she could before and that she is always tired. She is very sensitive to heat.

Fluoroscopic examinations of the heart shows it to be enlarged with the typical curve seen in auricular-fibrillation. As she does not have auricular fibrillation, this probably means that an endocarditis with poor nutrition of the heart muscles has been present for a long time.

Operation by the same technique as the previous one discloses a large colloid goiter with some areas of cystic degeneration. Removing the abnormal or degenerated portions leaves only a small thin layer on the posterior and inner portions of each lobe. This is all of the normal thyroid gland that has not undergone degeneration. If you will notice the specimen removed closely you will see that there are no normal areas of gland substance in it.

Notice here is a parathyroid just external to the capsule. It is as large as the end of my middle finger and almost an inch long. I really do not know whether we should remove this parathyroid or not. It is certainly not normal and yet it may be the only parathyroid that she has that is functioning. We will leave it and close as in the previous cases.

DR. DENNIS RUPP, Anaesthetist:

This patient had no preliminary hypodermic and was given ⅙ grain of Morphia ten minutes ago to prevent post-operative discomfort. The incision was made two minutes after the anaesthetic was started and she is perfectly conscious and repeats the vowel sounds now just three minutes after the Ethylene was discontinued.

DR. E. P. SLOAN:

This seventh case, Mrs. O. W. C., Bloomington, Illinois, age 29, has a small sclerotic thyroid. She gives a definite history of recurrent attacks of strumitis. During these attacks she is markedly toxic with severe heart symptoms. On examination we find her with a pulse rate of 148, basal metabolism rate plus 40 and with a pronounced endocarditis. The gland is small and hardly palpable. Her history is not clear as to whether her recurrent attacks of strumitis followed throat infection or tooth infection. She states that she always became better after having teeth pulled. Her tonsils are small, ragged, and show effects of previous abscess formation. We think that her remaining teeth should be pulled and that her tonsils should be removed.

Exposure of the gland confirms our diagnosis of sclerotic degenerated thyroid. This is the fourth goiter case this morning with definite history of strumitis or disturbance of the gland from infection.

I want you to notice that in all four of these cases that a large isthmus and long pyramidal lobe have been present.

We have now removed the pyramidal lobe, isthmus and the stumps of both lateral lobes, leaving but a very small amount of tissue on each lobe. This gland was not as large as a normal thyroid, but her heart and circulatory apparatus will improve promptly. The improvement in these cases is not in proportion to the amount of tissue removed. I am sure that this patient will derive as much benefit from operation as either one of the last two who had large goiters.

DR. WILLIAM YOUNG, Anaesthetist:

She has taken her Nitrous Oxide Oxygen very nicely. There has been no change in pulse rate, blood pressure, respiration or color.

DR. E. P. SLOAN:

This eighth case, Mrs. M. A., Murphysboro, Illinois, age 21. First noticed her goiter about 2½ years ago, while suffering from recurrent attacks of tonsilitis. After her tonsils were removed two years ago she thought her goiter was going to disappear. She states that it is not as large now as it was before her tonsils were removed. She had tremor of the fingers and tongue, with twitching of the eyelids developing about a year ago. At about the same time she noticed shortness of breath upon exertion, with considerable difficulty in swallowing, especially when tired. Tight feeling in the throat when lying on her back, bothered her a great deal. She says that she had to force herself to talk and swallow. That she is very nervous and that excitement will bring on the shortness of breath at any time. She has a pulse rate of 104, with characteristic heart sounds of endocarditis. The thyroid is smooth, rather soft and is located rather far back and downward in the supra-clavicular space.

Exposure discloses a rather large diffuse colloid with some nodular areas in the anterior portions of the lateral lobes, a long pyramidal lobe and a very much enlarged isthmus. You notice that the isthmus is quite tense, and yet upon separating its attachments it merely enlarges, and since the restricting effect of the capsule has been removed it is as soft as the rest of the gland. I am not clear as to just how much this condition is due to infection from the tonsils. The four cases that we have seen this morning that were clearly secondary to infections in the throat or teeth had some features in common with this one. However we have here a typical toxic colloid. I am certain that any pathologist would report this specimen to be that of a nodular colloid goiter.

We have removed the anterior two-thirds of the lateral lobes and the isthmus and the pyramidal lobe. We are sure that she will make a satisfactory recovery. If this is a genuine colloid goiter with nodular degeneration we feel certain that she will remain well. If this condition is due to strumitis or infection we will expect the remaining portions of the gland to cause trouble in a few years.

DR. DENNIS RUPP, Anaesthetist:

This patient had no preliminary hypodermic. Incision was made four minutes after the administration of Ethylene oxygen was begun. There has been no change in color, pulse rate, respiration. She was given ⅙ grain of Morphia twenty minutes ago, hypodermically. Two minutes from the time the mask was removed she was repeating the vowel sounds. Her voice is clear. She has swallowed saliva three or four times.

DR. E. P. SLOAN:

It is now 11:30 and we will adjourn to the Mennonite Hospital at 1 o'clock.

I hope that all of you gentlemen will be back here promptly at 4:00, because we have four nice operative cases for Dr. Crotti. Those of you who have not had the privilege of seeing Professor Theodore Kocher of Berne, Switzerland, "The Father of Goiter Surgery," and Professor Roux of Lausanne, the most spectacular operator that I have ever seen operate, will have the privilege of seeing Dr. Andre Crotti, use the best features of their technique. It is almost like seeing both of them operate, to see Dr. Crotti, who was assistant to each one for three years.

DR. MOSCHELLE:

I want to express my pleasure in the number who are here. Two hundred and fifteen are here, but all have not registered. I hope that all of you will join this Society and help us to bring together Surgeons, Internists, Anaesthetists, Pathologists, and Radiologists for study and exchange of views.

WEDNESDAY AFTERNOON, JANUARY 23, 1924.
MENNONITE HOSPITAL. 1:00 P. M.

DR. E. P. SLOAN:

I am glad to see so many of you here. I hope that you enjoyed your lunch and that you are rested. We have five cases for operation and in case we should not get through in time for you to get to Dr. Crotti's clinic on time, please have no hesitation in leaving, because I want all of you to see him operate.

Our first case is Miss Mable F. of Pekin. Age 27. She has a cyst of the right lobe and isthmus the size of a very large grape fruit. She has had what has been called a foetal adenoma since early childhood. One year ago it rapidly enlarged until it is causing severe pressure symptoms and is giving her considerable pain.

We make the incision and separate the muscles by the usual Sloan technique. We find a long pyramidal lobe, reaching up above the cricoid cartilage, which we separate from the surrounding structures down to the isthmus and release the short attachment of the right lobe to the trachea. By severing the isthmus at its junction to the left lobe and releasing the isthmus from the trachea, we should

be able to dislocate this tumor. We find it rather difficult, because the tumor, although released from its attachment to the trachea, is bound down by short attachments to the lower pole, and because of its rapid growth the blood vessels and other attachment at the poles have not had time to lengthen and are holding the tumor quite rigidly.

We will now cut some branches of the inferior thyroid at the lower pole, and without much trouble we succeed in dislocating the lower end of the tumor forward. Rotating it inward brings it out through the incision. You will notice that there is just room enough for the tumor to slip through the incision. Had we not separated the attachments of the tumor to the trachea we would have to do so now, and as you see there is practically no room to get to them, we would perhaps attempt to start at this outer border and then rotate it inward and get to those attachments from the outer side. By removing it in that manner the trachea would be rotated and tension placed upon the posterior attachments, while pressure would be made upon its anterior segment.

We now get to the thyroidea Ima, the posterior capsule and finally to the branches of the superior thyroid at the upper pole. Having tied the blood vessels, we inspect the left lobe. We are surprised to find an adenoma the size of a golf ball in this lobe. There are several small cysts in the anterior portion of this lobe, so we remove the anterior half, which includes all of the diseased portion.

We used Nitrous Oxide for four cases at St. Joseph's hospital this morning and Ethylene for four. We will use Ethylene for all the patients here this afternoon. You will notice the bright pinkish red color of the blood. It appears to me that while the patient is under Ethylene Anaesthesia the blood is of a lighter color than normal. Nitrous Oxide changes the blood to a bluish color, which is not cyanosis. You may have cyanosis also, but even when the patient is not cyanotic there is some bluish discoloration of the blood, due to the gas in the blood. It is really of no importance, but disturbs an operator until he gets used to it. We have been using Nitrous Oxide Oxygen anaesthesia here since 1908 with increasing satisfaction and increasing effectiveness. We have never had a death from it, and have never been able to see that any patient was harmed by it. Without a preliminary hypodermic it is not potent enough for satisfactory anaesthesia.

This patient had no preliminary hypodermic, and as you see she is perfectly relaxed under Ethylene. She was given a hypodermic of one-sixth grain of morphin when the operation was about half over, so that she will not have immediate post-operative pain and burning.

DR. E. P. SLOAN:

This second case, Mrs. O. L., Eureka, Illinois. This patient is 42 years old and has had a goiter since she was 18 years of age. From her history it was a diffuse smooth colloid for several years, markedly increasing in size during each one of her four pregnancies. After

the birth of her youngest child, 14 years ago, it became nodular. As you see, some of the nodules have broken down and formed cysts. She is not very toxic and has a well marked tremor. Her pulse rate is around 100. She has no palpitation, even upon exertion, although she says that she tires easily.

We make the exposure by the usual method, and you see it is almost impossible with the large tumor right in the way to get to the superior thyroid vessels. Therefore, we separate the superior border of the isthmus from the trachea and the inner attachments of the superior portions from the perilaryngeal structures. The gland is now mobilized to such an extent that it can be moved up and down in the neck for a space of nearly two inches without traction upon the trachea. Now we are ready to flex, and rotate and deliver the lobe. We will first flex, rotate and deliver the lower pole of the left lobe, clamp and sever the inferior pole, the inferior attachments of the isthmus to the trachea, and after the left lobe is delivered through the opening, we clamp and sever the posterior attachments entirely. We have nothing left except the branches of the superior thyroid. Ligating these permits us to sever the attachments of the superior pole and deliver this lobe through the small opening without cutting the muscle fibers. We now remove the right lobe in a similar manner, leaving, however, a small strip of gland tissue along in the posterior border that is apparently normal. We will finish the operation in the usual manner.

DR. DENNIS RUPP, Anaesthetist:

The patient anaesthetised in four minutes. Talked one minute after the mask was removed. Condition first class throughout.

DR. E. P. SLOAN:

This third case, Mrs. J. C., Eureka, Illinois, age 43, mother of three children, has had a goiter since she was ten years of age, markedly enlarged 12 years ago. It has been gradually getting larger ever since. She states that at the birth of her youngest child, 12 years ago she had palpitation of the heart, shortness of breath upon exertion and severe nervousness for three or four years. When the goiter became larger her symptoms disappeared to a great extent. She thinks that her general health is better now than it was 10 years ago. The cystic degeneration has destroyed a large portion of the gland substance, so she is probably right in her opinion.

Operation performed in a similar manner to the previous ones. The specimen removed is much larger than a quart cup and you can see the cysts scattered all through it. The larger ones are about the size of a small orange. The interesting point in this case is that the non-toxic diffuse colloid became nodular and toxic, that cystic degeneration occurred and large areas of the gland have been non-secreting since, with marked lessening of the symptoms. She has very little thyroid tissue left, but we anticipate no myxedema or hypothyroidism

in these cases. Theoretically speaking, they will occur, but practically they never do.

DR. DENNIS RUPP, Anaesthetist:

This patient has been an ideal Ethylene case. She went under in three minutes, but had very stertorous breathing. We inserted a breathing tube and her breathing has been perfectly regular and easy ever since. Two minutes after the Ethylene was discontinued she began to gag and we removed the breathing tube. Complete consciousness has returned and she has repeated the vowel sounds. There has been no change in color or pulse rate since the operation was begun.

DR. E. P. SLOAN:

This fourth case, Mrs. L. C. G., Weldon, Illinois, age 30, has a small atrophic gland. She is severely toxic, pulse rate of more than 130 all the time, basal metabolism plus 70. This attack is of only 5 weeks duration. She has a well marked endocarditis, but she has a blood pressure of 140. Ligation might help this patient some and she might get into a somewhat better condition for operation, but with the efficient circulation which she is maintaining and with a hemoglobin reading of 90, we consider a safe risk for operation. If we were to ligate, even though she became better, yet some damage would occur to her heart and circulatory system while waiting for improvement to occur.

This is a typical case of the kind of toxic goiter that ligation benefits the least. Injection of both lobes of the gland with Quinine and Urea-Hydrochloride solution would give more benefit than ligations, but the injection would have to be complete and would have to reach a very large portion of both lobes to have the desired effect.

We expose this gland in the usual manner. Because of its small size it offers little difficulty in removal. You notice that it is hard, granular, silghtly nodular, and that there is the characteristic change in the blood vessels that is always present in strumitis cases. The unusually large pyramidal lobe is surrounded by a plexus of enormously distended blood vessels. Ligation in this case would only very slightly lessen the blood supply, because these enlarged blood vessels near the pyramidal lobe would still furnish bountiful blood supply. We remove almost the entire gland and yet there is no normal tissue in the specimen removed. Closure made in the usual manner.

DR. DENNIS RUPP, Anaesthetist:

In three minutes after the anaesthetic was discontinued she was conscious and talking.

DR. SLOAN:

Gentlemen: It is now 3:30 and we are through with our fourth case. We will excuse you so that you can be in time for Dr. Crotti's operations at 4 o'clock.

REVIEW OF ANOTHER YEAR'S WORK IN THYROID DISEASE

FRANK H. LAHEY, M.D.

Professor of Clinical Surgery, Harvard Medical School

BOSTON

In a clinic where thyroid diseases may be observed in a large number of cases, and where it is studied by a group organized for this purpose, it seems worth while to present from time to time a brief summary of the work, with such deductions from it as we feel justified in drawing, based upon that work or upon our previous experience with the disease.

We have been impressed particularly in the last year with the fact that the seriousness of cases of thyroidism is being appreciated by the medical community at large, and that active measures to check the progress of the disease are being instituted eariler in an apparently much larger percentage of cases than heretofore, owing no doubt, to increased knowledge and wider interest in this subject.

We believe that fewer and fewer patients are being subjected to the so-called "rest" or medical treatment, a method with which we have but little sympathy, resulting, as it does, for these patients—most of whom can ill afford it—in a distinct loss of time and work and a very material loss in money. In a great many cases, unfortunately, the expenditure has not only been wasted, but the delay has brought the patient to operation a much poorer risk, often with a cardiac complication as a consequence of the postponement. Another sad feature of the wasted expenditure is that many of these patients come to operation only after their financial resources are exhausted. As far as the operation is concerned, this is of little importance, since facilities for the free care of such patients can always be arranged. Postoperative rest, however, with gradual resumption of activities, has been, in our experience, an essential factor in the complete recovery, and it is here that the evil effect of the economic loss is most evident. While free operative care and immediate postoperative care are always available for these patients, a period of rest without the necessity of wage-earning

is much more difficult and in many instances practically impossible to obtain, so that the patients often return to work much earlier than would be to their best advantage.

We have seen in the past years and still continue to see quite a considerable group of toxic cases who have been or are upon thyroid extract. We have recently had one case of primary hyperthyroidism who had received in large daily doses a total of two hundred and fifty grains of thyroid extract previous to coming to our clinic. Needless to say, her symptoms had been much intensified by this medication. Fortunately in a majority of cases the patients themselves appreciate that they are made worse by this medication, and voluntarily cease taking it. We have stressed on every possible occasion the perniciousness of this method of treatment; but again we wish to emphasize the fact that the administration of thyroid extract to toxic cases is dangerous, unjustifiable, and subject to possible serious consequences.

A somewhat similar point deserves emphasis also. The work with iodides of Kimball and Marine in Akron and its further application in Switzerland, with its possible diminution in the incidence of endemic goiter in goiter regions, offers a real boon to the residents in those regions. Yet, because of the improper comprehension of the minute doses required for this effect, there appears to be a tendency to give prolonged courses of iodide treatment, particularly to the non-toxic type of thyroid. That such prolonged iodine treatment may convert non-toxic into toxic goiter has been known for some time, and during the past year particularly we have on a few occasions seen cases in which this effect has been demonstrated. We, therefore, also wish to repeat and stress the fact that the prolonged administration of iodides may convert a simple non-toxic colloid goiter into an actively toxic one.

Basal metabolism estimations have continued to be not only of the greatest assistance but have proved of such increasing value to us that we cannot conceive of our being successful in conducting a thyroid clinic without this facility—so essential is it in the proper diagnosis and management of thyroid disease. We said last year that we did not believe that thyroid intoxication existed in the absence of an increase in the *true* basal metabolic rate. Of that we are increasingly sure, and we now feel

certain that when the basal metabolic rate fails to reach normal after thyroidectomy, a cure has not been accomplished, and some degree of hyperthyroidism still persists. Where this situation

RATE OF BASAL METABOLISM

Name—Miss C. G. Age, 18 years.
Diagnosis—*Primary Hyperthyroidism.*

Date	B.M.R.	Pulse Rate	Body Wt.	Operation
7-24-21	Plus 42	120-126	112.7 lbs.	
7-25-21				Ligation both superior poles.
8- 1-21	Plus 44	108-118	103.75 lbs.	
9- 5-21	Plus 40	98-104	112 lbs.	
9-13-21	Plus 39	108-112	113 lbs.	
9-14-21				Sub-total thyroidectomy.
9-27-21	Plus 25	78- 84	106.8 lbs.	
7- 7-22	Plus 31	80- 86	113 lbs.	
2- 8-22				Removal of thyroid tissue
7-14-22	Normal	76- 80	111 lbs.	from both lobes.
1-14-23	—10	60- 68	110.5 lbs.	

Chart showing persistent hyperthyroidism after sub-total thyroidectomy, with drop to normal after further removal of thyroid tissue.

exists, we have found that further removal of thyroid tissue has in most instances resulted in a clinical cure and a drop in basal metabolic rate to normal. We believe that the failure to obtain complete clinical cures by surgery in a certain percentage of cases in the past has been due either to insufficient removal of thyroid tissue (a consequence of natural timidity in the inexperienced thyroid operator) or to inaccuracies in diagnosis resulting in operation under the mistaken diagnosis of thyroidism upon patients with neurosis of non-thyroid origin. Elsewhere we have stated that if one accepts the dictum which we have had proved to us clinically and by many hundreds of pre- and postoperative basal metabolism estimations (we do postoperative follow up basal metabolisms on all thyroid cases, where possible, every two months for six months, and at the end of a year), that a drop to normal in the basal metabolism rate postoperatively occurs coincidently with a clinical cure, hence indicating the absence of hyperthyroidism, and no one dealing with these cases in large number properly checked by basal metabolism estimations can doubt this—if this dictum is accepted, then the absence of an increase in the basal metabolism rate preoperatively by the same logic indicates likewise the absence of a hyperthyroidism state. Having these facts in mind, and having also in mind the possible inaccuracies of diagnosis in the borderline cases, we desire to state our conviction that without *reliable* basal

metabolism estimations, dependable evidence as to pre-operative presence and postoperative absence of thyroidism cannot be obtained.

We have seen a few cases with normal metabolic rates in patients who were quite evidently in a period of remission of the disease. In such cases, with one exception, we have not operated unless there was clinical and metabolic evidence of a return of toxicity. (The one case operated was in a young man who had so many exacerbations of the disease that he was unable to retain a position long enough to obtain an occupation. Those attacks were sufficient in severity to require varying periods in bed and were clinically typical in character.) In general, it is our opinion that in the presence of a normal basal metabolism rate, it is unjustifiable to operate upon the word of someone else that thyroidism has existed in the past. It is better, we believe, to delay, unless some other indication be present, with the possibility that the remission may be prolonged into a permanent one, and to operate only upon definite evidence of a return of the disease.

It has again been our experience that basal metabolism rate alone is not a reliable guide to the extent of surgical procedure which the patient will endure. In reviewing our basal metabolism estimations upon one thousand cases, as would be expected, preliminary surgical measures were carried out upon most of the cases with excessively high basal metabolism rates, and complete surgical procedures upon most of those with low basal metabolism rates. If, however, the basal rate were permitted entirely to dictate the extent of the surgical procedure, many deaths would have occurred in those with relatively low rates if the complete operation had been done, and many patients with relatively high rates would have been subjected to an unnecessarily excessive number of divided surgical procedures.

We have seen several pre- and post-operative cases of persistently minus degrees of basal metabolism rate as low as —18 which could be elevated to normal by thyroid feeding, yet which did not demonstrably show evidence of myxoedema but appeared and felt better when their basal metabolism rate was elevated to normal by thyroid feeding. It seems possible that the basal metabolism reading may show degrees of thyroid secretion deficiencies which are not frankly evident.

We have again observed this year that following ligations even though there be clinical improvement as evidenced by gain in weight and drop in pulse rate, there frequently is little or no drop in basal metabolism rate. In practically all procedures in which any part of the gland is removed, however, an immediate lowering has occurred generally in proportion to the percentage of tissue removed.

We have continued to employ multiple stage measures in the serious cases, and feel even more certain that in the very intensely intoxicated cases it is a certain life-saving measure. Secondary thyroid operations may not be executed with the ease, dryness, and satisfactory appearance with which primary ones may. Since, however, their employment diminishes the mortality of the operation, as it undoubtedly does, the technical difficulties involved in them may be overcome through gentleness, patience and experience.

Elsewhere Dr. B. E. Hamilton, cardiologist to our clinic, has reported our experience in operating upon a group of decompensated cardiac cases with thyroidism. We believe that in this group of cases we have made more real progress in the past year or two than in any other group. Mention was not made of this group last year as a sufficient number of cases had not been done to justify conclusions. We have now operated upon forty-one cases of hyperthyroidism who have come to our clinic in varying degrees of decompensation, all incapacitated and many bedridden. With proper preoperative care they have been operated upon in stages, with but one case dying, and are all now able to be about and, in many instances, do a satisfactory amount of work.

Our efforts in the surgery of hyperthyroidism, in the past few years, have been directed largely toward the lowering of the mortality rate of the operation and the elimination of non-thyroid cases. This having been accomplished, we now feel that we have made real progress in another direction: by reaching out into this thyro-cardiac group which we have hitherto considered inoperable. As Dr. Hamilton has stated, we know of no other group of cardiac cases where it is possible to offer restoration of compensation to such a degree. It is particularly striking to see the capacity for sustained effort which these cardiac cases attain when relieved of their thyroid intoxication and persistent rapid

heart rate. There is almost no similar condition in cardiac disease where one may, by a surgical operation, remove a burden from the heart (tachycardia) which is so well calculated to use up its reserve and throw it out of normal rhythm.

We have had no tetany of any type during the last year, and have had but three cases of transitory tetany in all of our cases. We have had two cases of postoperative myxoedema, one not anticipated and one anticipated, in the removal of a large intrathoracic colloid mass in a patient previously operated elsewhere, the thyroid tissue in the normal location having been removed.

We believe that adherence to the technique published by us in Surgery, Gynaecology and Obstetrics will safeguard against hemorrhage and hematomata, two very distressing postoperative complications. We have never had a case of bilateral abductor paralysis.

During the year 1922, 450 thyroid operations were done upon 346 patients with but one death, making an operative mortality of 0.22% and a patient mortality of 0.28%. Of this group 75 patients had preliminary ligations and 271 had operations directly upon the thyroid gland. Of the 346 cases, there were 150 cases of primary hyperthyroidism, 67 cases of secondary hyperthyroidism, 115 of non-toxic goiter, 3 of thyro-glossal cysts and 5 of malignant thyroid. No cases were rejected as inoperable. Eight cases died before operations could be performed.

The only case dying during the year 1922 was one of colloid goiter in which a considerable portion of the goiter lay in the superior mediastinum and in which infection and mediastinitis occurred. Another case has also died of this disease already in the beginning of this year (1923). Previous to 1922, mediastinitis had never occurred in our clinic, in spite of the fact that the superior mediastinum had been opened a great many times in the removal of substernal and intrathoracic masses.

In both of these cases, we were not able to accomplish drainage or in any way limit the course of this infection, once it had become an established process.

Much has been written and at times almost a controversy has existed as to the relative merits of X-ray and surgery. The reports of Holmes and Means with accompanying metabolism charts indicate that it is possible in certain cases to accomplish

a lowering to normal of the basal metabolism rate, and the authors state a relief of symptoms. However, we are definitely opposed to X-ray treatment of thyroidism for the following reasons.

The purpose of X-ray treatment in thyroidism is to check thyroid secretion by destruction of thyroid tissue or by inhibition of secretory activity. This destruction of tissue, when it occurs, must be accomplished gropingly, striving to arrive at that desired point where enough thyroid tissue is prevented from secreting, so that hypersecretion is avoided, yet, where sufficient tissue is left unaffected so that myxoedema shall not result. We believe that such a method is not comparable in certainty and accuracy with surgical removal, where one may be sure of the amount removed, the amount remaining, and the supremely important factor of the activity of the type of tissue being dealt with. We further believe that our own unsatisfactory experience with removal of limited amounts of thyroid tissue may be repeated in many of the cases now considered cured by X-ray treatment. It has been repeatedly demonstrated to us that relief of hyperthyroidism for a considerable period of time may often be accomplished by hemi-thyroidectomy, but that recurrence frequently occurs in the remaining lobe.

Up to 1921 we employed an operation in which from two-thirds to one-half of one lobe of the thyroid was left. In a great majority of cases this accomplished an immediate relief of symptoms. We have, however, seen a considerable number of recurrences of hyperthyroidism in this remaining lobe of thyroid tissue, a condition which has been relieved by removal of a portion of the remaining lobe. So impressed have we become with the necessity of removal of large amounts of thyroid tissue for rapid, complete, and permanent relief, that we have in the past three years changed and adjusted the technique of our operation to meet this need, so that the smallest possible amount of thyroid tissue is left that will prevent the appearance of myxoedema. This, we believe, is essential if one is to produce a complete and lasting relief. As stated above, we cannot conceive of accuracy of X-ray dosage to such an extent as to be comparable with surgery in accomplishing this purpose.

Furthermore, during operations upon thyroids we are often surprised to find many cases possessing deep intrathoracic ex-

tensions whose presence we in no way suspected previous to operation. These we believe are a serious menace to life, and are in themselves an indication for surgery. Not infrequently, also, we have believed that a given case was of the hyperplastic, primary hyperthyroidism type, only to find at operation that it was a case of multiple adenomatous goiter with secondary hyperthyroidism. Both of these types of cases may not be discoverable by X-ray and the adenomata cannot, of course, be removed by X-ray.

As to mortality, we believe that the death rate in our clinic and in many of the large organized clinics, dealing with thyroids in numbers, is so low that it does not constitute an argument against surgery. In fact, the comparison of mortality in the two methods is by no means possible yet, as when X-ray treatment fails, the uncured patient is passed on to the surgeon for operation and any attendant risks.

We believe that the uncertainty of cure, the length of time necessary to ascertain the value of X-ray treatment in a given case, and the loss of time and money constitute weighty arguments against this form of treatment. We have repeatedly stated and firmly believe that hyperthyroidism is a sufficiently serious disease, and one so capable of being rapidly converted into a state in which operation is either extremely risky or not possible, that the method of treatment to be applied to it is the one which most quickly, most certainly, and most completely, removed the intoxication which produces the ill effects. That surgery meets that need far more satisfactorily than any other measure no one who has dealt with these cases in any number can doubt.

Further, we do not believe that the arguments against X-ray treatment are by any means offset by the stated benefits of this form of treatment, such as absence of scar, escape from operation, and avoidance of hospital stay.

Finally, we are absolutely convinced that centralization, individualization, and organization are the salvation of goiter cases which are to be treated surgically.

CONCLUSIONS.

Thyroid extract is contraindicated in toxic cases and prolonged iodine feeding may convert non-toxic into toxic goiter.

Hyperthyroidism does not exist in the absence of increased basal metabolism rate and cures of hyperthyroidism are not

accomplished without returns of basal metabolism rate to normal, provided there are no conditions other than a thyroidism elevating it.

Basal metabolism readings are of great value in neurosis simulating thyroidism, in that the true basal metabolism rate in the neurosis is normal.

Basal metabolism readings uncorrelated are not a reliable guide to the number of operations a patient will stand.

Minus degrees of basal metabolism rate may exist in patients free from clinical evidence of myxoedema, yet made subjectively better by raising the rate to normal with thyroid feeding.

Multiple stage measures are life-saving procedures in severe hyperthyroidism.

Thyro-cardiac cases first seen in decompensation may be restored to striking cardiac capacity if it is possible by thyroidectomy to remove the intoxication and to restore the heart rate to within normal limits.

The most dreaded, uncertain and uncontrollable factor in our clinic today is mediastinitis.

The moderate values of X-ray treatment are more than outweighed by its disadvantages.

Thyroid surgery done in a general surgical clinic equipped for the care and study of these cases will show few failures to cure and a mortality rate rarely over and in most cases under one percent.

AN ANALYSIS OF TYPES OF GOITER WITH INDICATIONS FOR TREATMENT

BY

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Goiter is not such an innocent disease as the public usually considers it. It is too seldom realized that goiter, especially in places where it is of endemic nature, influences not only the bodily but also the mental status of a people to an extent that no other endemic disease is known to affect them, and that goiter must therefore be considered as a national drawback.

We know too little concerning the etiology of goiter, yet we have means of curing the disease if recognized and treated early, but of this fact also the public is likewise too generally ignorant. There exist so many and partially justified fears of goiter treatment that many persons feel that it is best to leave a goiter alone. They regard it more as a physiologic condition than a disease.

It is therefore most urgent that doctors explain to a larger portion of the public that goiter *must be treated,* and treated *early,* or the progeny of those suffering from goiter will be threatened with the disease, and that such treatment need involve no danger to the patient if administered in the right manner and at the right time.

In the United States, in spite of repeated advice from physicians, nothing adequate has as yet been done in this matter. Many physicians have lately tried to emphasize the importance of such treatment in the schools. Among them may be mentioned Roux, Klinger, Weith, Fritsche, Kimball and Marine, but it is ridiculous to expect results after a few weeks of such treatment, as such rapid results could only be achieved from overdoses of iodine. Lasting results will come only by the use of small doses of iodine begun during early infancy and continued for a long period of time, perhaps even throughout life.

In this connection it is important to remember that goiter is a result of increased thyroid function. It is therefore clear

that during the period of greatest activity of the thyroid gland, goiter development will also be at its height and the goiter grow more rapidly. The thyroid function is at its height during the period of growth and development, and so we find the greatest number of goiters between the ages of 14 and 17 years, and in females this maximum really extends over the entire procreative period. The relation of thyroid function to the generative organs explains the greater frequency of goiter in the female sex. It is logical, therefore, that goiter treatment should be administered during the period of growth and development, and the popular prejudice against medical treatment during this time is not unjustified. Of course, over-doses of iodine at this period would be particularly harmful, but our physiologic treatment is not injurious but actually most useful during this period, as is to be expected.

CLASSIFICATION:

For purpose of study and treatment goiters may be classified as follows:

1. Colloid goiter
2. Adenoma of thyroid { a—Without hyperthyroidism / b—With hyperthyroidism
3. Graves disease

To the above classes of goiter we may add thyroiditis and the malignancies which may occur in either of the above three classes.

Colloid goiter is the type of goiter amenable to medical treatment, and is the type which occurs endemically in certain areas of the United States, especially in the drainage basin of the Great Lakes, of which this locality is a part. The exact cause is unknown, but lack of iodine is the most acceptable theory, and is supported by the excellent results from the administration of iodine in this type of goiter.

Colloid or endemic goiter usually appears between the ages of ten and fourteen years, and if untreated reaches its greatest size about the age of twenty-five. It is more frequent in the female than the male, and repeated pregnancies greatly aggravate the disease. We have seen this type of goiter, however, in several infants.

It may be recognized clinically as a *smooth, symmetrical* enlargement of the thyroid gland involving both lobes and the isthmus. It is never rough or irregular, and always appears before the age of twenty-five.

When small it produces no symptoms except that the patient may become anxious or worried over its presence. In the large goiters pressure symptoms may develop or various degrees of myxodema may result from pressure atrophy of the acinal cells.

In some cases, especially of females about the age of 16 or 18, nervous symptoms develop with tachycardia, tremors and fatigue. These cases are often treated as cases of hyperthyroidism, but as there is usually a gain in weight and the metabolic rate is normal or below, the differentiation should be easy. Many surgical misdemeanors have been committed in this small sub-group of cases.

In colloid goiter the acini of the thyroid gland are gradually distended and filled with an excessive amount of colloid. The normal cuboidal cells lining the acini are pressed out into a stratified layer and pressure atrophy develops so that their normal function of producing thyroxin is destroyed, and myxoedema of various degrees results, as previously stated. The effect on surrounding organs is usually the result of pressure; as for example,—hoarseness due to pressure on the recurrent laryngeal nerves and larynx, or a loss of elasticity in the trachea as the result of pressure of the colloid mass, with danger of tracheal collapse at time of operation.

Treatment of colloid or endemic goiter.

The ideal of medical research and effort is prevention rather than cure. We have therefore divided the subject of treatment into:

A. Prevention of goiter.

B. Treatment of already existing goiter.

A. Prevention of goiter. There are primarily two methods of preventing goiter formation. First, by drinking only water that has been boiled, and second, the administration of iodine.

Use of only boiled water.—Theodore Kocher first advocated that boiling the drinking water in goiter localities could prevent goiter. He also advocated at that time that the use of boiled drinking water should be obligatory in the public schools. This

method of prevention has never come into general use in the United States.

Administration of iodine.—By way of introduction we must state that all successful goiter medication contains iodine. Even when the medicine contains other substances, and iodine is not mentioned, it is always present if the medicine gives any results. We wish to particularly emphasize that in practically all of these iodine preparations the dose of iodine is too large.

The following methods have been used in our out-patient department at the hospital with good results, or have been advocated by experienced goiter therapeutists:

1. Iodized salt.—Ordinary table salt containing not more than 0.5 gms. or 7½ gr. of sodium iodide to the pound. We advise the family to use this salt instead of ordinary table salt as a routine unless some member of the family has an adenomatous goiter, in which case that person should use an individual salt cellar, as the administration of iodine in adenomatous goiters is likely to produce hyperthyroidism, as will be explained later.

2. Giving of 2 grms. or 30 grains of iodine spring and fall. —This method has been advocated by Marine, Lenhart and Crile. They usually advise the taking of this amount in a saturated solution over a two weeks' period of time. Occasionally symptoms of iodism will develop due to the large dosage. We do not feel that this method is practicable for general use.

3. Administration of tablets containing iodine in the schools. —This certainly would seem to be an ideal method. It would be more than the sporadic use of iodine as now practiced. It consists in the giving of a tablet containing 1/10 grain of iodine daily, five days in the week, and seven, eight or nine months in the year, depending upon the length of the school term. This dose may seem small, but it is sufficient to carry on the iodine metabolism of the thyroid gland. The tablets should be administered by the teacher at a definite time each day.

4. Inhalation of iodine.—This is a method in general use in Switzerland. Small vessels with perforated tops, containing salts of calcium, potassium and sodium iodide are exposed to the air, thus giving off the fumes into the air. If goiter is to be permanently avoided this inhalation of small amounts of iodine must be repeated and continued over long periods of time, or even throughout life.

5. The administration of thyroid gland preparation.—It has been found that dried thyroid substance from animals has a goiter-diminishing effect, and its significance in goiter pathology has been emphasized.

Can thyroid gland preparation be of use in prevention of goiter? That this is possible is no longer open to question, but this method has greater difficulties than those encountered in iodine administration, as in large doses it is even more injurious than iodine. As we are dealing with an organic substance, and as the animal glands from which the extract is made vary widely in their chemical composition, accurate dosage is difficult. Of course, none but an assayed preparation should ever be used.

The use of thyroid extract in the prevention of goiter has, however, an important place. It is indicated when signs of diminished thyroid function have been observed in the goiter of a goitrous family; that is, in families where goiter has existed for generations. In such cases it is strongly urged to treat the pregnant women with thyroid extract so that the children may not be born with goiter, a goiter tendency, or what is still worse, with a thyroid deficiency.

In such children iodine prophylaxis for goiter does not suffice, and they must be treated with thyroid extract from early infancy, if the thyroid function is to be kept normal and the child is to develop normally, mentally and physically.

Such treatment should only be administered under constant supervision of a physician, and never by druggists or parents without medical advice.

B. The treatment of already existing goiter.

1. *Treatment of goiter with iodine.*

It is, of course, much easier to prevent a goiter from developing than it is to cure one already formed, especially as goiters lead to degeneration. It has been shown by several workers that the thyroid gland shows an increase of degenerated tissue with each successive exacerbation. Iodine has less effect on degenerate tissue than on normal tissue, so that in order to be successful, goiter treatment must be instituted early. One other consideration must be taken into account if the goiter is to be cured, i. e., to disappear, and that is that iodine must be taken in continuous *small doses*. Practically this is not so easy, however, because people lack the necessary patience. If they see no imme-

diate result they discontinue the treatment, and too often resort to some of the numerous quack treatments for goiter. The result of such treatments is a rapid disappearance of the goiter, but, alas, also a just as rapid recurrence with a progressively diminishing effect of the intensive iodine treatment for every recurrence. It has been proved by the author, by Baumgarten, des Ligneris, Marine and Lenhart, that such large doses of iodine injure the normal thyroid tissue even more than they affect the abnormal tissue, and cause degeneration.

As we have mentioned before, iodine loses its efficacy when the tissue is degenerate, but this is not the worst result of treatment of goiter with large doses of iodine. Much more serious are the effects produced on the general condition of the patient. Iodism and hyperthyroidism have already been mentioned in this connection when too large doses of iodine were used in the effort to prevent goiter. Even worse effects are produced when a goiter already exists. Only too often the patient loses in strength and health as rapidly as the goiter disappears; he loses weight, becomes violently excitable, with a rapid pulse and high tension heart beats, with sweating diarrhea, sleeplessness and great weariness. In other words, he has developed what Theodor Kocher calls "Iodine Basedow's Disease," which lasts for months, and may leave permanent heart trouble.

Probably the administration of iodized salt is the treatment of choice, as it can be safely continued throughout life. When after several years it becomes unnecessary for the parent, the treatment should still be kept up for the children as a prophylactic measure.

One of the methods of giving iodine,—that is the iodine ointment which is applied by rubbing on the skin over the thyroid, is only mentioned to *condemn it.* In the first place, massage of an active goiter is bad treatment. Secondly, you cannot estimate the amount of iodine which the patient is getting.

3. *The Treatment of goiter with animal thyroid extract.*

P. Bruns demonstrated for the first time in 1895 that the administration of dried thyroid substance could cause disappearance of goiter. Five years previously Murray discovered that in individuals lacking the thyroid gland, by regular administration of animal thyroid substance the serious symptoms resulting from such a lack should be materially benefited.

The reducing effect of thyroid substance in goiter depends on a similar action as it acts as a substitute for the thyroid whose function has been disturbed by the goiter, and thus decreases the tendency to goiter development.

There is still another indication for treatment of goiter with thyroid extract. When degeneration of the goitrous tissue takes place, which may occur as a result of overdoses of iodine, the organism, in spite or the enlargement of this organ, is no longer able to produce enough thyroxin. The results of this impaired thyroid function now begin to tell on the general condition. The symptoms are numerous. They show themselves principally as bodily and mental fatigue, in faulty circulation, neuralgia and rheumatic pains. Many goiter patients suffer from these symptoms, and may be benefited by treatment with thyroid extract. Usually they are treated with all kinds of remedies with no result, as they themselves as well as the physician too often ascribe these symptoms to other causes. It cannot be too often repeated that such thyroid therapy must not be attempted without the direction of a well-informed physician.

The adenomatous or nodular goiter is the most common type of goiter needing surgical treatment. It can be conveniently divided into two sub-classes for study—simple adenoma and adenoma with hyperthyroidism. This type usually develops about the age of puberty. It may grow slowly or rapidly, and frequently produces the pendulous goiter so often seen, while a small adenoma occurring in the isthmus of the thyroid may cause serious embarrassment to the breathing. The adenomata are usually multiple, and clinically are recognized by multiple hard, irregular and movable nodules occurring within the thyroid gland, although some of them may be soft and cystic. In contrast to the symmetrical colloid type they are usually asymmetrical enlargements. They may remain quiescent for years and produce no symptoms, or they may become rapidly toxic following any of the acute infections such as tonsillitis, influenza, pneumonia, etc. They are frequently "lighted up," so to speak, by the injudicious use of iodine, either internally or externally. Their treatment is definitely surgical, but operative interference should be avoided, especially before the age of twenty-five, since during the developing period of life the thyroid is most essential. But should pressure, deformity or toxicity develop, a

double resection should be performed, conserving as large an amount of thyroid as possible, since some adenomatous tissue must be left, while in older individuals all adenomatous nodules would be removed. Recurrence is, of course, more likely when operated early before a more complete removal can be performed.

Adenoma with hyperthyroidism usually occurs in individuals who have had the adenoma in the thyroid gland for several years, without symptoms. They usually become toxic following one of the acute infections and are frequently not recognized. They may be recognized clinically by marked cardiovascular changes, rapid loss in weight, gastro-intestinal symptoms, increased metabolism and increased nervous excitability. The presence of the above symptoms without a palpable thyroid enlargement in the neck should suggest the possibility of an intra-thoracic goiter or other accessory goiters. Following partial thyroidectomy, the metabolic rate rapidly returns to normal, and the gain in weight is quite rapid. Of course, if the cardiovascular disturbance is well marked and anatomic changes have occurred, the restoration to normal will not be complete. The results of *early* operation in adenoma with hyperthyroidism are 100% if we rule out the accidents of surgery, namely, hemorrhage, infection and embolus.

The results are not so good if the toxicity has been excited by repeated courses of iodine therapy. Strange as it may seem, we still see many cases of adenoma, with or without hyperthyroidism being treated by iodine. This form of treatment of this group of cases, especially in individuals past thirty-five years of age, cannot be too strongly condemned.

Exophthalmic goiter or Graves disease is characterized by a definite train of signs and symptoms, the most prominent of which are tachycardia, exophthalmos, muscular tremor, weakness, vasomotor, excitability, disorders of metabolism, and many manifestations of disturbances of the nervous system which are associated with hyperplasia of the thyroid gland, and in many cases by disturbances in other glands of the endocrine system. A small group shows definite hyperplasia of the thymus gland which should be excluded before surgical intervention is advised. An X-ray examination to exclude this complication should be a routine procedure. On one of our own cases, with only slight improvement after thyroidectomy, further X-ray examination

disclosed a large thymus, and following X-ray therapy there was prompt and satisfactory recovery.

The exact etiology of Graves disease is unknown, but infections, nervous shock and thyroid toxins seem to be the chief causes.

Clinically, there seem to be two types of this disease; the one, characterized by its chronicity, is gradual in onset and runs an even, usually mild course, and rarely develops a thyroid crisis; the other, sometimes called the remittent type, is characterized by one or more fulminating attacks induced by shock, fright, sickness, overwork, acute infections, and so forth.

The symptoms of the latter group gradually increase in severity, with or without the appearance of goiter or exophthalmos, until a crisis occurs, which is characterized by the sudden exacerbation of the symptoms, with the addition of nausea, vomiting, diarrhea and extreme debility. If the patient survives the crisis, a period of partial remission of the symptoms follows which may persist for months, but is usually followed by recurrence of varying intensity. The remission may, however, be complete, with the patient symptomatically cured, the disease being quiescent, or the remission may be only partial, with chronic invalidism.

Medical treatment of Graves disease is still advised by some internists. It consists of rest in bed, ice cap to the heart and the thyroid gland, low protein diet, and administration of lugols solution gtts. 10 daily. If, after a conservative trial of four to six weeks, the patient has not markedly improved as evidenced by gain in weight, slowing of pulse and recovery of nervous equilibrium, it should be discontinued and surgery advised.

X-ray treatment has been tried by several clinicians of repute, but the larger goiter clinics have discontinued its use. It should never be used except in the hyperplastic cases—Graves disease. Definite dosage is problematical and the destruction of the thyroid tissue cannot be estimated or controlled. We have seen one case of tetany result from X-ray treatment. Our results have been disappointing, and do not compare favorably with surgery.

The treatment is surgical, but all cases cannot be subjected to operation by any set rule; each case must be individualized, and herein lies the whole solution of this difficult class of cases.

A certain percentage of cases will seem to recover without treatment, while others run an acute course, and terminate fatally in spite of all treatment.

An analysis of statistics from various clinics would seem to indicate that seventy percent are cured by surgery, twenty percent are improved, and ten percent are not benefited or have recurrences.

Iodin in Public Water Supply.—Rochester, N. Y., is attempting to solve its goiter problem by putting iodin in the public water supply. Water from Hemlock Lake, which flows into Rush reservoir about ten miles south of Rochester, has a normal iodin content of about 1 to 2 parts per billion. This is increased to about 50 parts per billion by the addition of sodium iodid. The amount of water entering the reservoir is determined at the Gate House by means of a "thin edged weir" or dam. The city was using when iodin was added about 25 million gallons of water a day, to which 16.6 pounds of sodium iodid was added daily for three weeks. The salt was simply placed in a cotton bag and held in the water above the dam until dissolved, which required about three or four minutes. The cost is estimated at about 1 cent per person per year, using the iodin salt six weeks in the year. A resurvey will be made next year to determine the results obtained.—Copied from A. M. A. Journal, Nov. 17, 1923.

DIFFERENTIAL DIAGNOSIS OF INCIPIENT TUBERCULOSIS AND INCIPIENT GOITER

BY

ROSWELL PETTITT

OTTAWA, ILL.

Ten days ago I had an opportunity of making the rounds in the Mayo Clinic, Service of Dr. Plummer, and saw there probably one hundred cases of goiter. I mentioned to Dr. Walter Boothby, who is associated with Dr. Plummer, that I was on the program to speak before this Society on "The Differential Diagnosis of Incipient Goiter and Incipient Tuberculosis." He was rather surprised that there should be any difficulty in differentiating the two conditions; that there are certain symptoms that clearly differentiate the early goiter and certain other symptoms that clearly distinguished the early case of tuberculosis. However true this may be, mistakes are very frequently made.

I happen to be the Director of the Ottawa Tuberculosis Sanatorium, an institution for the treatment of pulmonary tuberculosis. In this sanatorium we have forty-five patients at the present time, and three of these patients have scars on their necks of previous goiter operations. All three of these cases have at this time definite physical signs of pulmonary tuberculosis. Is it possible that in these three instances an early tuberculosis was mistaken for early goiter, or is it possible that they had both tuberculosis and goiter? That, of course, I do not know. However, if they had pulmonary tuberculosis at the time of the operation it can be stated without question of contradiction that the shock of the operation was certainly not beneficial, and probably harmful to the patient's resistance to tuberculosis. On the other hand, how frequently is early goiter mistaken for pulmonary tuberculosis?

In 1921, Dr. Gay (Reports U. S. P. H. S.), went over the records of 1700 cases in which a diagnosis of pulmonary tuberculosis had been made, and in these 1700 cases he found 176 mistakes, or 10.4 per cent. In this group of 176 cases he found that 32 had chronic bronchitis; 18 had cardiac disturbances; 15

had upper respiratory tract infections; 15 had neurasthenia; 12 were suffering from interstitial pneumonia; 10 were cases of bronchiectasis; 11 were non-tuberculous infections of the lungs; there were four cases of asthma; four cases of lung abscesses; and three cases of gastric ulcer, and of this total number of 176 cases, four were ultimately diagnosed as hyperthyroidism, or in the latter instance an error of 4/10 per cent. This is indeed a small error, but one that must be taken into account, and the possibility of mistaking an early tuberculosis for an early goiter must always be kept in mind.

From my own experience, however, in seeing cases admitted to a sanatorium for the treatment of pulmonary tuberculosis, and from the statistics above quoted, I think it reasonable to assume that there is a higher percentage of error being made by goiter specialists and general surgeons in mistaking early tuberculosis for early goiter than there is on the part of internists and specialists in tuberculosis in calling early goiter an early tuberculosis. Can the two diseases be readily differentiated? In many cases, it is true that they can be, where active symptoms of the disease are present; such, for instance, as well-marked physical signs in the chest, typical temperature curve, definite X-ray findings in the lungs, tubercle bacilli in the sputum, etc., should not, under any circumstances, be confused with goiter. It is also true that in cases of well-marked hyperthyroidism that a diagnosis can be made across the room, but this is not true in the early case.

What are the symptoms of early tuberculosis? Lassitude, fatigue, loss of appetite, fever, loss of weight, and weakness. These can also be the symptoms of early goiter. In addition, however, there are other symptoms in goiter that we do not have in tuberculosis ordinarily, such as tremor, palpitation, and increased appetite.

It may be interesting to list in parallel columns the prominent symptoms in the incipient stage of both diseases.

SYMPTOMS OF	
Tuberculosis	Goiter
Fatigue, lassitude, lack of appetite.	Fatigue, lassitude, increased appetite.
Weakness, nervousness, fever.	Weakness, nervousness, no fever.
Rapid pulse, loss of weight, cough, night sweats, dysponoea.	Rapid pulse, loss of weight, cough, sweating, dysponoea.
	Palpitation, tremor.

On the basis of these two groups of symptoms there are certain things, particularly palpitation, tremor, heart changes, and increased appetite that are almost always present in toxic goiter that readily differentiate the early goiter from the incipient tuberculosis, if a careful history is taken.

When the basal metabolic rate was introduced I was immediately impressed with its possible value as a method of differentiating tuberculosis from goiter. In my experience with it, however, during the past two years, the results have been unsatisfactory. I have made determinations of the basal metabolic rate in forty-five cases of early pulmonary tuberculosis. Three successive determinations were made in each case on three successive days. All of the determinations were made by the same technician under exactly the same conditions. In a majority of these cases it was found that the metabolic rate was ten per cent below normal. In several instances, however, the rate was plus ten per cent. In several instances, however, the rate was plus ten per cent to plus forty-five per cent. In these cases the determinations were repeated with exactly the same results as before. There were no signs of goiter. From these determinations I was forced to conclude that either our method and technician were unreliable, or that we were dealing with cases in which tuberculosis and goiter were both present. I am inclined to believe that our aberrant results were due to poor technique rather than the presence of the two diseases, as there were no confirmatory signs of goiter present in any of these cases. Perhaps if we had used a better apparatus, such as the Haldane-Tissot, rather than the Handy Benedict, our results would have been more reliable, but who is there in a tuberculosis sanitarium that has the time to carry out elaborate gas analysis determinations?

Until an accurate, simple method of determination of the basal metabolic rate can be perfected, it will be impossible for the ordinary practitioner to utilize this method as a general diagnostic test.

I am of the opinion, however, that a careful study of the symptoms in any case will make it possible for us to make an accurate, differential diagnosis between incipient goiter and in-

cipient tuberculosis, and by more careful study, perhaps, we will be able to keep some cases of incipient goiter out of the sanitarium for the treatment of tuberculosis, and we may likewise be able to save a number of cases of early pulmonary tuberculosis from operations for goiter. We must, however, keep in mind that it is possible for an early case of tuberculosis to also be suffering from goiter, or a case of goiter may also be afflicted with pulmonary tuberculosis.

THE ROENTGEN TREATMENT OF TOXIC GOITER

EDWARD W. ROWE, B.Sc., M.D.

LINCOLN, NEB.

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INTRODUCTION

No discussion on the treatment of goiter should fail to pay tribute to the names of those pioneers whose names stand like milestones in the historical survey of goiter. In 1786 Parry recognized exophthalmic goiter. Graves in England in 1835, and Basedow in Germany in 1843, studied it more carefully. Moebius in 1886 brought forth the theory that the morbid function of the thyroid caused an intoxication. He called it hyperthyroidization, which is the syndrome today spoken of as hyperthyroidism or thyroid intoxication.

Recent literature is fresh with the reports of thyroid research. Let me call attention to the large number of articles in current literature on the roentgen treatment of thyroid intoxication. Within the last ten years the advancement in knowledge of the chemistry, the histopathology, the physiology and the classification of thyroid disease has no parallel in medical science.

Kendall in 1914 separated a pure chemical compound thyroxin from the thyroid gland. Subsequently he proved that thyroxin is the active principle of the thyroid gland, and demonstrated the chemical composition of this compound. Plummer by his sagacious reasoning has correlated the recent findings of science and has developed a new philosophy of the disease, which in the main has been acceptable. With the added interest in metabolic studies of the alterations in metabolic

rates by certain thyroid states, the work of Boothby and Sandiford at Rochester, DuBois at Cornell, Harris and Benedict at Carnegie Institute, Deyer at Oxford, England, and others have completed work of great practical value. The researches in this country of Halsted, Cunningham, Carlson, Marine and Cannon are worthy of our greatest admiration.

PATHOLOGY

A relative view of all thyroid diseases is necessary to treat thyroid intoxication. Plummer's clinical classification is chosen because of its wide adoption and its comprehension.

1. Diffuse colloid goiter.
2. Adenomatous goiter with hyperthyroidism.
3. Adenomatous goiter without hyperthyroidism.
4. Exophthalmic goiter.
5. Myxedema.
6. Cretinism.
7. Childhood myxedema.
8. Thyroiditis.
9. Malignant disease of the thyroid.

Some of these names represent pathological conditions and some clinical conditions. In fact, each name represents a disease with its etiology, pathology, symptom complex, prognosis and treatment.

Certain anatomical considerations should be kept in mind. The thyroid gland is ductless. Its secretion communicates with the outside tissue only through its walls. It consists of epithelial tissue bound in a capsule-like lymphoid tissue. It is dumbbell in shape, lying across the trachea, with the bar below the larynx, both lobes investing the trachea. It is abundantly supplied by blood vessels and nerves buried deep in the vital tissues of the neck. The normal gland consists of acini containing colloid and lined with relative inactive cuboidal columnar epithelium, supported by connective tissue similar to that of other parenchymatous organs. The gland is abundantly supplied with reserve tissue. Three-fourths of it has been removed without any demonstrable disturbance in the physiology of the body or any change in the glandular tissue of the remaining thyroid. The thyroid undergoes periods of activity and repose, stores iodin and colloid. In periods of stress it uses stored iodin and delivers thyroxin to the blood stream. The

mechanism of stimulation is not known. To one accustomed to viewing secreting microscopic sections of glands, it has the appearance of a quiet inactive gland.

In the examination of thyroid tissue there is nothing pathonomonic to tell of the presence of thyroid intoxication or exophthalmic goiter, nor to indicate the clinical state or degree of intoxication. Hypertrophy and hyperplasia are found in characteristic manner in adenomatous and exophthalmic goiter, but at the same time they are sometimes present in other types and cause no thyroid intoxication.

However, the pathological findings are fairly constant and reduce themselves to simple types, with all other tissue changes but degree of modification. The primary types found are—colloidal, adenomatous, and exophthalmic. Or, colloidal, nodular, and diffuse, showing hypertrophy and hyperplasia.

In the colloid type there is an increase in the intra-alveolar colloid. In the adenomatous new cells develop usually localized but often diffuse, thought by some to be embryonic resting cells and hence liable to perverted cell activity. Diffuse parenchymatous hypertrophy, symmetrically involving the entire gland together with hyperplasia, is the characteristic type of so-called exophthalmic goiter. But three primary pathological processes are possible—hypertrophy of the alveolar epithelium, increase in intra-alveolar colloid, and development of new alveoli. Hyalinization, cystic degeneration, fibrous formation, calcification and malignancy may arise, but are incidental to the primary pathological changes that may occur in any glandular degeneration or new growth.

The physiological changes associated with these pathological changes are:

1. Hyperthyroidism, or that syndrome which is identical with the administration of thyroxin and rarely seen except where hypertropic or adenomatous changes in the thyroid are found.

2. Hypothyroidism, or that syndrome which may be considered the opposite condition, and causing a symptom complex, varying in degree but occurring as thyroxin is depleted in the tissue.

3. Exophthalmic goiter, which may be called a hyperthyroid state plus something yet in controversy as to cause and action, but giving the well known signs.

Cunningham and Carlson in trying to produce experimental thyroidism found that the administration of thyroid extract never produced exophthalmic goiter. Cannon produced some of the signs of exophthalmic goiter by anastamosis of the phrenic and cervical sympathetic nerves. Marine's experiments reproducing the same work were unsuccessful. "The experiments were so carefully done that, at present, the various hypotheses, assuming lesions in the sympathetic nerves and especially in the cervical ganglia as accountable for the disease or for hyperplasia of the gland are without experimental foundation." (Nellis B. Foster.)

We are compelled for the present to fall back upon the theory advanced by Plummer, that the explanation of hyperthyroidism in exophthalmic goiter lies in the production not of thyroxin, but of an incomplete molecule slightly different in chemical composition.

THYMUS

The thymus gland is normally of little significance in the adult. Its extirpation in animals is known to have brought about no detectable change in any body function or organ. Its rôle in the thyroid disease is not known, but its presence in sixty-five per cent of the cases of exophthalmic goiter operations and its importance in roentgen treatment, make it very probable that some pathological process in it goes along with thyroid disease.

Marine in 1888 suggested the regrowth of the thymus in Graves' disease. Thymic hyperplasia is now recognized as frequent. Blackford noted it in all younger individuals afflicted with Graves' disease. He believes that a persistent thymus is one of the characteristic findings in thyroid intoxication, the average weight in twenty-four cases being thirty-six grams. Thymus hypertrophy is usually found in all cases up to forty. Beyond the fourth decade an enlarged thymus occurs in perhaps half of the cases that come to autopsy. This persistence of the thymus is not characteristic of the toxic form of goiter, since it is occasionally found with simple or colloid goiter.

Blackford summarizes that every patient under forty with thyrotoxicosis, and every patient under thirty with simple (colloid) goiter examined postmortem showed evidence of hypertrophy of the thymus. Over forty years of age one-half of

the cases of thyrotoxicosis and three-quarters of the cases of colloid goiter showed enlarged thymus at postmortem.

THYROXIN

The normal action of the thyroid influences growth of the skeleton, the activity of all tissues, including the central nervous system, secondary sex characteristics and mature life. It controls metabolism. Its interrelations with other glands are problems yet for study.

The disturbance in physiology and the developing syndromes of the various thyroid diseases may be understood in terms of thyroxin. The story of thyroid intoxication is locked up in the knowledge of the composition, elaboration, storage, liberation and action in the body tissues of the chemical compound thyroxin. This important compound is manufactured in the thyroid gland and may be found in the body tissues in very minute quantities. The thyroid has no other known function than to produce thyroxin. It is stored in the colloid of the gland. The function of thyroxin seems to be to activate the function of the body cells or to furnish actual energy. When in excess hyperthyroidism is the result, and the basal metabolism rate is above normal. When it is low or absent, the metabolic rate is low.

METABOLISM

Disorders of the thyroid gland are differentiated today by alterations in the basal metabolism rate. An increase or a decrease in the thyroxin output is accurately gauged by this method, giving the true status of severity. The basal metabolism rate is the mathematical expression representing the basal heat production of an individual under standard conditions. It is like the thermometer, measuring the heat phenomena inherent in the living organism. Workers in clinical calorimetry differentiate three classes of metabolic rate—normal, increased, or diminished. For practical purposes, plus 10 to minus 10 may be considered normal or a possible variation due to the method or the difference in technique. Minus 10 to minus 40 are low ranges or pathological thyroid. Plus 10 to plus 125 are the possible high ranges.

In health, variations are slight. The basal rate is more constant than the pulse or temperature. The slightest change in the chemistry of the blood causes the most grave disturbance.

The changes in the iodin content of the thyroid are comparable in delicacy.

Of the diseases so far investigated, the following are characterized by an increased metabolic rate: Exophthalmic goiter, hyperthyroidism of adenoma, the actual stage of acromegaly, and all febrile conditions. In other diseases, such as essential hypertension, pernicious anemia, leukemia, diabetes, and possibly a few others not yet investigated, a basal metabolic rate lightly above normal may occasionally though consistently be met with. After more than 20,000 tests for basal metabolism by Boothby, and his co-workers, it was found that 95 per cent of all abnormally increased basal metabolism rates are due to hyperthyroidism, either exophthalmic in type or from thyroid adenoma, if a febrile condition is eliminated by the thermometer. Then for practical purposes an increased basal metabolic rate means exophthalmic goiter or adenoma of the thyroid, or some mixed type, providing the factors enumerated have been eliminated. Of particular value is the metabolic rate in the elimination of those cases called circulatory asthenia, effort syndrome, disordered action of the heart, cardiac neurosis or nervous instability or neurasthenia. In these conditions the basal metabolism is not disturbed.

The metabolism test may be called the quantitative estimation of the thyroid function. It is the gauge for treatment. It helps the clinician to visualize the progress a patient is mak ing. It clinches the diagnosis in doubtful cases.

For one treating a large number of thyroid cases, the use of the metabolimeter is a necessity. Like the microscope and the electrocardiograph, it is necessary for the one who needs it. Even long experience with the clinical signs of hyperthyroidism does not develop accuracy in estimation of the metabolic rate. Experience gives qualitative skill, but not quantitative ability.

MEDICAL TREATMENT

The object of treatment in thyroid intoxication is threefold —to reduce the output of thyroxin from the gland, to permanently lessen the function, and to conserve the other organs of the body.

Essential in every case is the task of cleaning up all focal infection. These should be treated in a radical manner and thoroughly eradicated. The number of cases of thyroidism de-

veloping following chronic and acute focal infection is so great that the evidence is strong for the theory of focal infection activating the gland. Tonsils, teeth, paranasal sinuses and the more remote gall bladders and appendices should not be overlooked.

The general management of the case is of major importance. Most patients will be ambulatory and remain in their homes. The environment should be free from anxieties and family cares and from false suggestions. The psychic control should be complete. The patient should be relieved from laborious duties and responsibility. If the patient can be hospitalized for a time the united improvement from rest and isolation will be of advantage. The diet should be nutritious. A glass of milk three or four times a day is desirable. The caloric intake must equal or exceed the output as nearly as possible.

Rest and diet may relieve entirely the mild cases, but after the metabolic rate has been brought to a certain point no amount of rest or drugs has any influence over the initial advantage. Aconite and quinine derivatives have no influence on the metabolism rate. They are like many other drugs which have been carried over from empirical medicine. Digitalis may be of value if there is decompensation from muscular failure and dilatation. It seems easier to introduce than to discard valueless drugs, yet there are many copied from one text-book to another.

SURGICAL TREATMENT

All that has been said applies to the general treatment of every case. Nothing more may be necessary in the mild forms of toxicity, but moderate, severe or repeating mild cases demand more effective treatment. Two methods of choice are given—surgery and roentgen treatment. The surgery of the thyroid has been widely adopted. The continental surgeons, especially Kocher and Mikulicz, prepared the way in the last century. The work of Halsted, Charles Mayo and Crile, in this country, has added a brilliant chapter to surgery. Since the adoption of the subtotal thyroidectomy technic the results have improved and the recurrences are fewer. This type of operation has raised the per cent of cure in one clinic (Mayo) twenty per cent. But there is still much uncertainty about the type of operation to choose and about when to operate. A master in this field of surgery has said that a successful operation only

begins the treatment. Until the time is ripe for operation the patient is either left to fret, or receives only that amount of improvement which rest can give. The destruction in the vital organs goes on. Surgery has a definite risk. Crile and Mayo may claim less than one per cent mortality from operation. This is in selected cases. Excellent surgeons under the best conditions admit five per cent. My own opinion is that the general run of good surgeons have a much higher mortality than these masters' statistics.

It is impossible to compare in a practical manner the per cent of cures by surgery and the roentgen ray. Neither speak the same language. Statistics are largely dominated by surgeons. Halsted gives 60 per cent cures in his 500 cases. Judd reporting on 121 cases six years after operation, concludes that 45 per cent were cured, 23 per cent practically cured. Haudek and Kiser give the failures in surgery on the continent as 10 to 27 per cent, from roentgen treatment 10 to 25 per cent. These failures are due to insufficient removal of gland by surgery or an insufficient roentgenization, and the presence of an abnormal pluriglandular constitution. They state that the recurrence after operation is 4.68 per cent, and after roentgen therapy it is the same. The fact is that few are completely cured. The clinical signs may disappear and the metabolism rate return to normal, but there remains a subnormal individual whose capacity in life is restricted. Instability and neurasthenic symptoms leave marks of the original disorder.

The method of choice must rest upon the risk involved, the selection of patients, and the economic condition of patients. General satisfaction of methods rests on clinical observation of results. The real development of roentgen therapy has only existed since 1914, when the Coolidge tube and standard equipment made it possible to accurately administer and reproduce dosage. Unfortunately sufficient time has not yet elapsed for roentgen statistics to show ultimate results. We can only examine those that are available and these are indeed hopeful.

The most outstanding reports come from the Massachusetts General Hospital. There for a half dozen years cases of hyperthyroidism have been studied from three viewpoints—the internist's, the surgeon's and roentgenologist's. The results are familiar to all. But, in comparing roentgen therapy and sur-

gery it was found that in the third year after treatment the end results were the same. In roentgen therapy the improvement was gradual and progressive, with surgery there was a sudden marked improvement and a subsequent relapse. The factor of rest was distinctly greater in the surgical group, yet no more ultimate benefit was secured. The chance of cure in exophthalmic goiter was no better with surgery than roentgen ray, and the risk was greater.

Surgeons offer objections to roentgen therapy:

1. That it does not produce permanent cures. Neither does surgery in a large per cent. Our statistics that are accumulating indicate that the cures about equal surgery when they are at all comparable.

2. That cardiovascular renal changes go on to the detriment of the patient. This is probably no more true in roentgen therapy than in surgery, for the surgeon selects his cases, does not operate on the crest or a rising metabolic curve.

3. That subsequent operations are more difficult. This objection is probably without foundation. It is denied by fair minded surgeons. Some others often use it for an excuse when their technique is poor. Adhesions, if present, are generally due to thyroiditis or perithyroiditis or previous surgery, especially ligations.

4. That the danger of hypothyroidism is great. Theoretically it should be as easy to carry out roentgenization as extirpation. Practically this danger rarely occurs. I found two or three cases in the literature where the metabolic rate had been reduced to an abnormal degree. Two of these took thyroid tablets and later returned to normal. It is well known that thyroid patients even untreated, may fluctuate below normal. In defense I also offer a patient's history treated for hyperthyroidism and extensive carcinoma of the thyroid gland. She has had short wave length therapy, three times the E. S. D. for treatment of the malignant goiter. It was given in desperate doses for over two years. It is now five years, the patient is alive, in good health and her basal metabolism is only ten minus.

ROENTGEN TREATMENT

The effects of roentgen rays are upon the thyroid gland. There is a slow degeneration of the parenchymatous tissue,

which is replaced by fibrous tissue if a sufficient number of radiations over a long period of time are employed. Since the gland is ductless there is no way to determine visually the reduction of the gland secretion, but there are good reasons to conclude that there is a diminution. Theoretically there is a field for roentgen therapy. Like surgery, it decreases the output of the gland. Analogy suggests this and clinical observation and the metabolic reading support the belief. The pathological effect of roentgen rays on tissue is controlled by the amount. Roentgenization can by judicious choice be carried to any logical point.

In the hands of an expert the dangers of roentgen treatment are small. Telangiectasis and atrophy of the skin seldom if ever occur if the dose is kept below an erythema skin dose. Prevention of untoward skin effects is by filtration and sufficient skin distance. Hypothyroidism is not a danger if the basal metabolism rate is recorded regularly.

The earlier the toxic goiter is treated the more prompt is the relief. Younger patients as a rule do better. A timely course of treatments may serve to prevent an established career of hyperthyroidism. Old cases of hyperthyroidism require a long rest after the roentgen treatment. There is no such thing as an innocent pathological goiter. These glands with any change whatever in them should be watched and treated whenever hyperthyroidism arises.

The first sign of improvement comes in about three or four weeks, when the patient reports improvement in the general bodily feelings. It is a frank statement admitted by the patient. Next will be noticed a fall in the pulse rate; then the weight begins to gain. Nervousness and insomnia improve. In about fifty per cent the exophthalmos eventually disappears. In most cases it improves. The thyroid enlargement is the last objective sign to go.

Its disappearance is frequent but on account of the pathology in the gland seldom complete. The end results depend entirely on the harm which has resulted to the human machine. Young individuals under thirty-five years show wonderful recuperative powers. The length of treatment must be guided entirely by the clinical symptoms and the metabolism rate.

The roentgenologist must have the full co-operation of the

patient. Many failures occur because some one else directs the case and the specialist is the technician. The one who directs the roentgen treatment must have full charge of the therapy. Either he is able to direct the entire management, or he is not fit to operate a switch in the treatment. It requires broad medical experience and high degree of expertness. This does not preclude a careful diagnostic study of the case, nor frequent consultations with any other expert. The patient's case must not be taken for a week, a month or for any limited time.

The indications for roentgen therapy may be grouped as follows:

1. All exophthalmic goiters not at too high a metabolic reading. The roentgen treatment may be cautiously started in those much too high for surgery.

2. To prepare for surgery by reducing the activity of the thyroid. Experience shows that few of them change to surgical treatment.

3. After surgical failure.

4. Adolescent goiter not responding to rest.

5. Adenomatous goiter with toxicity. Surgery may relieve the patient more quickly, but some of the satisfactory cases are in this class.

6. Carcinomatous degeneration after surgical removal accompanied by toxicity.

The contraindications are:

1. Colloid, cystic, fibrous and nodular goiter without toxicity.

2. Goiter causing marked pressure in the neck without symptoms.

3. Intrathoracic goiter.

Pfahler of Philadelphia has reported 200 cases of toxic goiter which he has treated with uniformly good results. He concludes that "Radiotherapy is the best form of treatment for toxic goiter," and the results are "equal to surgery."

Christie and Groover report 157 cases with results equal to surgery. They say, "The roentgen method is being used by an increasingly large number of internists, but very few surgeons have as yet been willing to give this method a sufficient trial."

Allison reports 27 cases treated by roentgen ray. Of these 24 were cured clinically and according to metabolic readings. Three came to operation. One was definitely improved, and the other two were a few months afterwards.

Upson at Battle Creek reports on 130 cases. Before the roentgen treatment the average metabolic rate was plus 38. After treatment it was plus 15. The highest rate observed before treatment was plus 110. After treatment plus 38, and the lowest minus 11. Average weight before treatment was 116½ pounds, after 127 pounds. Average pulse rate before treatment 98, after 83. He found that four-fifths of the cases have symmetrical involvement of the gland. Those who were able to carry out a plan of rest, medicine and physiotherapy, got well after the cessation of irradiation.

My own experience has been with 50 cases which have had a diagnostic study, consultation with internist and surgeon, a careful estimation of metabolism rate and frequent checking during the treatment. The majority have received but one series of roentgen therapy extending over three to five months. About one-fourth have required a second shorter series on the appearance of another hyperthyroid wave. Five have had several series over two years. All have been benefited. The gain in weight, the lowering of the pulse rate, the reduction in the metabolic rate have all been uniform. None of these have changed to surgery, though at any time I have been open to advise it if the patient wished it or if it was thought more feasible. Ten per cent of the group have had previous surgery. But three have been refused, two for economic reasons (they chose the shorter route, surgery), one for acute hyperthyroidism.

This work has been done in a general surgical and medical clinic with the full co-operation of the staff.

The method of treatment is to administer the rays over three areas—both lobes and the thymus. The first four treatments are one week apart. In the second and third months they are ten days apart. Then there is usually a period of rest, and subsequent administration is determined by the metabolism rate. After treatment is discontinued the patient is advised to report at least every ninety days. The kilovolts used are 80, the distance 35 c.m., and the filters 5 m.m. Al. This is very similar to the Pfahler technique laid down by him in 1915.

Massive therapy in large doses, except in malignancy, is never used.

CONCLUSIONS

1. Clinical observation and the records of basal metabolism indicate that properly selected cases are as rationally treated by roentgen ray as surgery.

2. The general management of patients is as important in roentgen treatment as in surgery.

3. Adenoma with toxicity yields more quickly to surgery, but often roentgen treatment gives early and brilliant results.

4. Exophthalmic goiter shows best results of all types. If the roentgen treatment is faithfully carried out it seldom requires surgery, while the results are just as permanent.

5. There is no mortality, no fear of operation, and no defacing scar on neck.

6. The treatment of toxic goiter is major roentgenological work and demands broad medical experience.

7. The estimation of the basal metabolism rate is necessary to accurately determine the degree of toxicity and to visualize the progress of the disease.

SUMMARY

There has been great advancement in the knowledge of thyroid disease. The number of patients seeking relief by nonsurgical means is large. It is important to determine by scientific methods the value of treatment by roentgen ray. The surgeons are somewhat hostile to this treatment, chiefly because roentgenologists have entered into direct competition with them in a field that has been largely surgical. Internists have seized upon the method of treatment and are offering assistance by studies in metabolism and the problems which have to deal with the treatment of thyroid disease. The whole problem of thyroid intoxication is bound up with the problem of the manufacture, storage and use of thyroxin or a similar compound which is a chemical production of the thyroid gland. The many types of pathological changes in the thyroid gland may be summed up as colloidal, adenomatous, and exophthalmic. All other changes are but the usual tissue changes which might occur in any organ under the same circumstances. There are no pathognomonic changes determining the state of thyrotoxicosis. Many case records illustrated by charts show by pulse,

weight and metabolism the changes which patients undergo while taking the roentgen treatment. It is definitely observed as the opinion based on this study, that the X-ray will accomplish as much as the surgery. It may require a longer time, but the results are just as good and the mortality is nil. Most types of toxic goiters are amenable to roentgen therapy. The contraindications are: (1) Colloid, cystic, fibrous and nodular goiter, without toxicity. (2) Goiter causing marked pressure with symptoms. (3) Intrathoracic goiter. The treatment of thyroid intoxication is major roentgenological work. Improvement is first noticed by a reduction of pulse rate, increase in weight, improvement in nervousness and insomnia. In about fifty per cent the exophthalmos will eventually disappear. In most cases it improves. In some it does not appear. Thyroid enlargement is one of the last objective signs to disappear. The end results depend entirely on the damage done, when the hyperthyroidism has disappeared. If degeneration of heart muscle and nephritis occur, improvement is often great, but a complete cure cannot be expected where these changes have occurred. All patients should have metabolism rate taken both for diagnostic purposes and from time to time in order to follow the treatment. The roentgenologist must follow his own cases. He must be capable of more than technical administration of the dose. He must have a broad knowledge of disease and an up-to-date conception of how to treat thyroid intoxication. Rest, isolation, psychic control, diet and eradication of focal infection are as much the duty of the roentgenologist to prescribe and follow up as is the administration of roentgen ray.

BIBLIOGRAPHY

Allison, R. G.: "Thyroid Therapy." Minnesota Med., July, 1922, p. 404.

Allison, R. G., Beard, A. H., and McKinley, G. A.: "X-ray Treatment of Toxic Goiter." Am. J. Roentgenol., Nov., 1921, p. 635.

Aub, J. C., Bright, E. M., and Uridil, J.: "Mechanism of Increased Metabolism in Hyperthyroidism." Am. J. Physiol., July, 1922, p. 300.

Boothby, Walter M.: "The Basal Metabolic Rate in Hyperthyroidism." J. A. M. A., July 23, 1921, p. 252.

Boothby, Walter M.: "Diagnosis and Treatment of the Diseases of the Thyroid Gland." Oxford Med., Vol. III, p. 883.

Boggs, Russel: "Treatment of Goiter by Radiation." Am. J. Roentgenol., Dec., 1919.

Cottenot, C.: "Roentgen Treatment of Exophthalmic Goiter." Medicine, Paris, p. 542.

Editorial, Journal American Medical Association, Nov. 12, 1921.

Fischer, J. F.: "Roentgen Ray Therapy of Exophthalmic Goiter." Ugesk, f. Laeger, April 13, 1922, p. 345.

Foster, Nellis B.: "Diseases of Thyroid Gland." Nelson's Loose Leaf Medicine, Vol. III, and "Summary of Literature," p. 246.

Holmes, G. W., Merrill, A. S.: "The Treatment of Thyrotoxicosis by Roentgen Ray." J. A. M. A., Nov. 29, 1919, p. 1693.

Hubeny, N. J.: "X-ray Treatment of Exophthalmic Goiter." Bulletin Chicago Medical Society, Feb. 28, 1920.

Judd, E. S.: "Results of Surgical Treatment of Exophthalmic Goiter." New York State J. Med., Sept., 1920, p. 287.

Lichty, John A.: "The Treatment of Thyroid and Other Endocrine Disturbances as Viewed by the Internist." Am. J. M. Sc., June, 1920, p. 159.

Lichty, John A.: "Treatment of Diseases of the Thyroid." Am. J. Roentgenol., Dec., 1919.

Means, J. H.: "The Determination of the Basal Metabolism." J. A. M. A., July 30, 1922, p. 347.

Means, J. H.: "Hyperthyroidism." M. Clinics N. America, Jan., 1920, p. 1077.

Means, J. H., and Aub, J. C.: "The Basal Metabolism in Exophthalmic Goiter." Archives of Internal Med., Dec. 15, 1919.

Plummer, H. S.: "Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body. J. A. M. A., July 23, 1921, p. 243.

Park, A., and McClure, R. O.: "Results of Thymus Extirpation in Dogs." Am. J. Dis. of Child, Nov. 19, 1919.

Reiley, W. E.: "The Treatment of Goiter by X-ray." Penn. J. of Roentgenol., Oct., 1921, p. 22.

Roth, N.: "After Roentgen Exposures in Exophthalmic Goiter." Wien. Arch. f. inn. Med., Jan., 1922, p. 367.

Seymour, Malcolm: "Myxedema Following Treatment of Graves' Disease With Roentgen Ray." Boston M. & S. J., Sept. 1, 1921, p. 261.

Sistrunk, W. E.: "Indications for Surgical Treatment in Various Types of Goiter." Surg. Gynec. & Obst., Oct., 1921, p. 348.

Soiland, Albert: "Radiation and Thyroid Disease." J. Radiol., July, 1921, p. 19.

Trosler, J. S.: "The X-ray Treatment of Basedow's Disease." The American Physician, April, 1921, p. 289.

Upson, W. O.: "Radiation Therapy of Hyperthyroidism." J. Michigan M. Soc., Sept., 1922, p. 381.

Van Allen, H. W.: "Hyperthyroidism, Basal Metabolism and Radiography." J. Radiol., March, 1922, p. 83.

Williams, C.: "Classification of Goiter: an Analysis of 100 Cases." Am. J. M. Sc., Feb., 1921, p. 223.

Witherbee, W. D.: "X-ray Treatment of Tonsils and Adenoids Associated With Exophthalmic Goiter and Tubercular Glands." X-ray Bulletin, Treatment Dept., U. S. P. H. S., June, 1921.

RADIUM THERAPY OF THYROID

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I have been treating goiter, in an experimental way, with radium for the past four years. During this time I treated every case that came under my observation, and this included practically every known type.

My results have been that a change was noticed in about forty-five per cent of the cases treated,—thirty-five per cent were regarded as cured and most of the cases treated were not benefited at all.

In treating thyroids, it is quite necessary to make a careful and accurate diagnosis,—for the thing of prime importance to the patient is the benefit to be obtained from such a treatment.

For this reason and for the interest of radiologists I have divided the different types of goiter into two main groups:

(1) Cases with hyperthyroidism.

(2) Cases without hyperthyroidism.

(a) Types of cases mentioned in the first group are:

Exophthalmic
Hyperthyroidism with goiter
Hyperthyroidism without goiter

(b) Those placed in the second group are:

Cystic
Colloid
Simple
Adolescent
Malignant
Intrathoracic

Cases in the first group may be treated with radium; those in the second group should never be. In other words, the percentage of cases that are to be benefited will be found only in the first group. Those in the second group not only receive no benefit, but the treatment may, indeed, prove harmful.

The benefit to be received by cases in the first group depends upon the ability of the radium rays to produce an inhibition or abolition of the secretory function of the gland or even the complete destruction of the secreting cells themselves. It is conclusive, then, that the treatment is indicated where there is an excessive secretion from the thyroid.

Cases in the second group in which radium is contraindicated,—a state of atrophy of the normal gland is produced, resulting in hypothyroidism. The size of the gland is much less affected in cases of this group than it is in cases of the first group.

The gland, at most, is not reduced completely after radiation, since the secretory cells are partially replaced by fibrous tissue, thus preventing a reduction to a normal sized gland. A reduction of two and one-half inches in the circumference of the neck is about the average.

While the metabolism test may mean little to the surgeon, I regard it as quite essential to the radiologist, as it serves as one of the many guides to a lessening in the degree of thyroid toxicosis that is gradually and continually taking place over the whole period of treatment,—usually three months. The metabolic rate at this time should be within the radius of normal. (No more than 15 plus or no less than 15 minus.)

The same is true of the blood picture. A hemoglobin, differential red and white blood count, is made, as a routine, at six different times during the treatment period of three months, and the change that takes place is most interesting.

As regards to the technique of application,—I block out the neck in four squares,—one over each lobe, one over the isthmus and one over the thymus. This makes four areas to treat. Usually 100 milligrams of radium is used. The radium element is encased in silver tubes 0.5 mm. wall thickness, and is further screened with 1.0 mm. of brass with two to three millimeters of rubber and mounted on a block of wood about an inch thick.

This is held in position with adhesive tape for four hours over each square. The procedure is the same for all cases, for the first treatment, and acts as a so-called "feeler" to determine the patient's susceptibility to radium rays. To those cases that are inclined to be radium immune, the dosage is relatively

increased over each lobe area. At least one-half lethal dose should be given at this time.

If there is no marked improvement as shown by the metabolism test and clinically, after three months' radiation, the case should be referred to the surgeon for operation. If the case is slightly improved, but not well, radiation should be continued at long intervals and the medical and hygienic treatment persisted in until the patient returns to normal.

ILLUSTRATIVE CASES

The cards I have with me represent 100 cases of the first group. I am going to pass them out so that you may see for yourself the very interesting picture they make on paper. Two sides of the history card is shown as in illustration. At the top of the front side is the name of the patient, address, case number, date, present history, previous history, diagnosis, previous treatment and by whom referred. The squares to the left represent the squares as they are blocked out on the neck and the space to the right is provided for a double check on the nurse in charge, for the time, milligram hours and the screening. The figures 1, 2, 3 represent the first, second and third treatments. Hours, marked at the top for each change of radium is given by a figure in each square. Figures on the reverse side correspond to the figure 1, 2, 3 on the front side and give you the changes in the blood picture at the time of each treatment.

Case No. 1—A woman of thirty-seven years, married and the mother of four children, the youngest being six years of age. About six years ago she noticed an enlargement of the thyroid and was later verified as a goiter by her family physician and since that time her symptoms gradually grew worse. She was extremely nervous, slept poorly and the mornings found her exhausted and disinclined to work. Her digestion was bad and she complained of choking spells. The usual eye symptoms were present.

Examination revealed a thyroid definitely enlarged, involving both lateral lobes, and measured seventeen inches in circumference. Her pulse rate 115, increased on slight exertion—metabolic rate was 72 plus. Her red cells numbered 3,172,000 whites 8,400. Hemoglobin 60%. I gave her a radiation every other day during a week's stay at the hospital, for three exposures for a total of 1500 milligram hours. She was then given

rest for thirty days and when she returned, the circumference of her neck was diminished two inches—metabolic rate was 45 plus and pulse 88. The choking spells had entirely disappeared and her nervousness and tachycardia were markedly improved. When she came back thirty days later, for her third treatment her metabolic rate was normal, her red count increased to 4,620,000. Her neck measurement was 14½ inches. The goiter had reduced in size until it was hardly noticeable and when I last heard from her in December 1923, practically three years later, she was in good health and her weight in that time increased twelve pounds.

Case No. 2.—This is a case of hyperthyroidism without goiter. A woman of thirty-one years and had previously had excellent health. About a year ago she developed nervousness, tachycardia and exophthalmus. She complained of headache along with her menses which were irregular. Loss of energy, sleeplessness, palpitation on slight exertion, tremor, digestive disturbance, profuse sweating at nights and gradual loss of weight. Her metabolic rate was 45 plus. While I do not depend entirely on the metabolism test, it is most essential to determine a diagnosis in many cases, especially the ones where many of the symptoms are masked and a plus metabolism will greatly assist in a diagnosis. In a case of this kind,—hyperthyroidism without goiter—attention to the teeth, tonsils and digestion is of prime importance. This patient was given 2000 mgh. in the course of a week's treatment. She went home for thirty days and when she returned she had made a gain of five pounds and was feeling very much improved. By the time she had taken her third radiation three months later she had gained fourteen pounds and had no complaints.

Case No. 3—This is one of the exophthalmic goiter who give a history of influenza (intestinal type) in 1919, as did many others of the same type. She had the enlargement of the thyroid gland and protuberance of the eye balls along with the other recognized symptoms of severe hyperthyroidism. This was in 1922—three years following her attack of influenza. She began by having attacks of vomiting and was easily excited and nervous, with very rapid heart action on exertion. Her red count was 4,060,000 whites 11,600 hemoglobin 60%, metabolic rate 60 plus. In January, 1922, I gave her 2000 mghs. dur-

ing her week at the hospital, and when she returned for her last treatment in April, same year, I gave her 3000 mghs. She made a gain of twelve pounds since her first treatment in January. Protuberance of the eyes had entirely disappeared, nervousness, tremor, and palpitation were only recognizable on exertion. The last time I heard from her family physician she was still in excellent health.

Case record card illustrated below

GENERAL REFERRING CARD

RADIUM DEPARTMENT

Name—Mrs. E. H. Case No. 812.

Address—Hartsburg, Illinois. Date, July 10, 1923.

Previous History—Childbirth, 1918. Influenza, 1918.

Present Condition—Local, both lateral lobes enlarged. General, nervousness, tachycardia, tremor.

Diagnosis—Clinical, exophthalmic goiter. Previous treatment, none. Referred by Dr. H. H.

Hours	Time	Mgh.	Screening
1.—4 4 4	8, 12, 4, 8	600	1 in. wood, 2 mm. lead, 1 rub.
4 4 4	8, 12, 4, 8	600	
2.—4 2 4	9, 1, 3, 7	500	
4 2 4	8, 12, 2, 6	500	
3.—6 6	8, 2, 8	600	
6 6	8, 2, 8	600	
		3400	

Age, 23; sex, female; weight, 118-133; height, 63; circ., 15-14-13; B. P., 112, 118, 118; B. Metabolism 7 or †, 70, 32, 12.

BLOOD

Date	Rbc.	Wbc.	Hgl.	Pl.	Ml.	Ll.	Sl.	Ci.	E.	B.
July 11, 1923	3340000	15000	65	52	12	12	23	0.98	7	1%
	3715000	11600	65	83	..	6	8	0.88	.	3%
Aug. 16, 1923	4120000	10400	75	54	2	5	37	0.91	.	2%
	4160000	11200	75	71	4	6	16	0.91	.	3%
Oct. 15, 1923	4500000	7800	75	60	2	7	27	0.83	.	3%
	4620000	10000	75	82	2	5	11	0.81	.	2%

Pulse, 120-92-82.

USE OF SEAWEED IN THE PREVENTION AND TREATMENT OF GOITER.

J. W. TURRENTINE, Ph.D.

WASHINGTON, D. C.

Iodine existing on the earth in forms that are mostly highly soluble in water, the bulk of it is to be found in the sea whither it has been deposited by drainage water. In the rocks which have their origins in the sea, some traces of iodine remain and in the drainage waters flowing over and through them. This small trace diminishes in concentration as the tops of drainage areas are approached, there the soils being more thoroughly leached out. The same is true of thin strata of soils overlying impermeable rocks. Thus, higher concentrations are found in soils and drainage waters occurring nearer the ocean, although here undoubtedly drainage is only one factor as the supply of iodine is prevented from disappearing there through additions gained from sea spray blown inland.

Iodine is sea water, as stated by Hayhurst in his comprehensive article, "The Present-Day Sources of Common Salt in Relation to Public Health and Especially to Iodine Scarcity and Goiter,"* quoting Molinari, exists to the extent of 0.01 gm. iodine (calculated to NaI) per liter, and, quoting Gautier, occurs in three forms, for the most part in organic combinations dissolved in the sea water, a small portion also in the organic form, in sea organisms, and a further small portion in the inorganic form, but occurring only at great depths.

When land deposits of sodium chloride were developed through the desiccation of sea water and the crystallization of sea salts, iodine salts were not deposited, both because of their extreme solubility and likewise their extremely low concentration in sea water as compared with that of the salts deposited. So, even here, where the desiccated products of sea water are found in enormous quantities and in great varieties, iodine is almost entirely absent; and as pointed out by Hayhurst, in preparing these salines for human use, both in the manufacture of

* J. Am. Med. Assn. 78, 18 (Jan. 7, 1922).

salt for dietary purpose and other salines for fertilizer purposes, the salts are refined and impurities, particularly the more soluble ones, such as iodine salts, are carefully and completely eliminated. Thus from soils where they would not be expected and from salines where they would be, iodine salts are thoroughly removed.

Small and varying amounts of iodine are found in plants, and in the animals feeding upon them. The occurrence of iodine in food materials has been studied by Forbes and Beegle,† especially from the point of view of goiter. While they find that there is not a sufficient divergence of iodine content of the foods grown in goitrous and non-goitrous regions to account for the varying incidence of that disease, they point out "the smallness of the proportion of our food products which contain iodine, the minute quantities in which iodine is ordinarily found and the haphazard nature of its distribution."

Just as the soils occurring near the ocean contain more iodine, so it is to be expected that the plants growing thereon will likewise and it is shown by Hunter and Simpson, as stated by McCarrison, that the thyroids of sheep grazing near the ocean contain more iodine than those grazing inland.

But the occurrence of iodine to a remarkable degree in plants is confined to those that grow in the sea. In certain sea plants the iodine content, as will be shown, is phenomenal.

The foregoing suffices to show the intimate manner in which the normal supply of iodine for the metabolic use of the human body is linked with the sea. And in this connection it may be suggested that in this fact is found a bio-chemical bit of evidence in support of the theory of evolution, or at least that part which hypothesizes a marine origin of animal life. Our early metabolism being established on the basis of chemical elements available or always present in that medium of existence, it has not been possible yet to evolve a new system of life processes which can do without these elements. McClendon* voices the same idea in a different manner when he says:

"It has been considered by some biologists and chemists that living matter originated in the sea and the elements of living matter correspond to those found in the sea water. We might

† Bull. 299, Ohio Agr. Expt. Sta.

* "Are Iodines Food?" Science 55, 1423 (April 7, 1922).

look, therefore, to the composition of sea water for the elements we should expect to find in living matter."

He accordingly, recognizing the general iodine deficiency in the diet of the average man and appraising the possible value of the other ingredients of sea water, advocates the use of unrefined sea salt as a condiment or diet amendment and shows how it may be prepared in a non-hygroscopic form not disagreeable to the taste.† In this he is ably supported by Hayhurst who says—"Of the dependable sources of iodine in nature—sea air, sea food and sea water—it is to sea water * * * that inland dwellers should look. This substitution would appear to offer a complete solution to the iodine deficiency problem, if nothing else, while evidence would tend to show that other constituents of sea water have an undoubted place in the economy of the higher animal organism, perhaps to the extent of precluding some diseases which are likewise, possibly, of a deficiency type."

Entirely in support of this evident close relationship between goiter and the sea are the goiter maps based on the observations of the draft boards during the last war.* The data on which they are drawn show that the incidence of simple goiter varies from 1.02 among men residing near the sea to 17.55 among those from inland regions. They illustrate the increasing incidence as tops of drainage areas, the Appalachians, the Great Lakes regions, and the Rocky Mountain regions, particularly the Pacific Northwest, are approached.

In entire accord with these data are the striking observations of McClendon showing a parallelism between goiter incidence and the absence of iodine from drinking water.

It will be noted, by a comparison of the respective maps for simple goiter and exophthalmic goiter, that there is a remarkable coincidence in proportional incidence. While there is no etiologic connection so far recognized between these two forms of thyroid derangement, here is a phenomenon that demands explanation. The two are regarded by some as opposites of each other, yet both are derangements of the thyroid gland and both exhibit a deficiency of iodine in the gland. They occur side by side, the general conditions that induce one—so far as these condi-

† See also a later article by McClendon, "Simple Goiter as a Result of Iodine Deficiency," J. A. M. A., **80** (1923), 600.

* Defects of Drafted Men. War Dept. Publication.

tions are understood—inducing the other. Both are the result of hyperactivity. In one the hyperactivity takes the form of hyperplasia, while in the other, of excessive secretion. Are they the opposites of each other, or are they different manifestations of the same thing? One is demonstrably the result of iodine deficiency. Can we escape the conclusion that the other is also?

LACK OF IODINE IN NORMAL DIET

The modern diet is made up of highly refined materials. Seeds constitute most of it. These, in their normal state, in addition to materials of great value as sources of energy, contain many of the mineral elements and compounds essential to animal life and growth. But in most cases they are refined to the point where the latter are eliminated. As a result they are not able to sustain life; and it has been shown that animals fed on certain of them exclusively perish more quickly than do those entirely without food. The excessive use of refined foods leads to deficiency diseases. In this category are those diseases induced by a deficiency in the vitamines, now receiving most marked attention, and of a joint deficiency in vitamines and other things, as a lime-vitamine deficiency; amino acid deficiencies, as in pellagra and deficiencies in the various inorganic or mineral elements of food less well recognized. There are some fourteen elements which at present are regarded as essential to the economy of the human body, which are calcium, magnesium, iron, sodium, potassium, chlorine, iodine, fluorine, phosphorus, sulphur, carbon, hydrogen, oxygen, nitrogen. Very conspicuous in point of number (though not of quantity) are the so-called mineral elements. Contained largely in the skins and husks of the common food materials they are generally eliminated. Over refinement in food manufacture accordingly deprives us of these essential elements which under less artificial conditions would be a natural part of our diet. No automatic method is provided for supplying these materials of great importance in every case, but of the greatest importance in connection with the feeding of the young. The diseases of the bones in growing children as a result of deficiencies, particularly of calcium and phosphorus, are well recognized. Less attention is paid to the frailty and inadequacy of the teeth as a result probably of similar causes.

Together with deficiencies of the many commoner elements, there occurs of course, an even more marked deficiency of iodine. The occurrence of iodine in food materials is well shown by the elaborate research of Forbes and Beegle as summarized in the following table:

	Total number of samples	Number containing iodine
Animal products	35	13
Cereals	378	60
Fruits	34	5
Garden vegetables and root crops	131	39
Hays, silage and forage crops	205	50
Leguminous seeds	32	11
Manufactured foods, and milling and manufactory by-products	25	13
Nuts	7	0
Sea weeds	2	2
Spices, condiments and stimulants	27	2
Water	2	2

This summary shows that the various groups analyzed, in the order of the increasing frequency of iodine occurrence, may be arranged as follows: (1) Nuts; (2) spices, condiments and stimulants; (3) fruits; (4) cereals; (5) hogs, silage and forage crops; (6) garden vegetables and root crops; (7) leguminous seeds; (8) animal products; and (9) manufactured foods and milling and manufacturing by-products. "Among the cereals iodine was found as an uncommon constituent, usually in traces only."

METHOD OF SUPPLYING IODINE TO THE DIET

As a source of iodine for human metabolism it is obvious one must look to the sea, the great storehouse of that essential element and choose that method of securing the requisite quantity in the manner which most readily coincides with one's already established dietary habits. Sea foods might well become a more common article of diet but at the present cost for preservation and transportation do not reach the majority of people. Sea salt is not a commodity at present obtainable on the market but its wide introduction as a condiment would be of great benefit to the human race. A logical and from many points of view an ideal conveyor of all these essential elements are the kelps, the larger sea weeds of the brown algae group.

COMPOSITION OF KELP

In recent years, and on occasions in earlier years, a great deal of study has been devoted to the composition of kelp. The

literature is replete with references to these investigations. Kelps have been studied from the point of view of their utilization as foods, and as carriers of inorganic salts and of iodine.* The different species vary in chemical composition, quantitatively rather than qualitatively. Most of the work of recent years has been devoted to the single giant kelp of the Pacific, the Macrocystis Pyrifera, which has been the main basis of the extensive investigations of the U. S. Department of Agriculture. Its composition is more thoroughly understood perhaps than that of any other kelp.

The composition of this kelp has been studied to determine its water, organic, inorganic, nitrogen, protein, sugar and fat content. It is tremendously complex, being made up of a great variety of organic and inorganic compounds and of organic compounds containing and probably combined with mineral elements. In organic combinations are parts at least of the iodine, the phosphorus and the sulfur. All of them are held in varying degree in collodial suspension in the plant.

A great many analyses of Macrocystis Pyifera have been made in State and Federal laboratories, mostly to determine its inorganic content. These show on the average: Potassium chloride, 22%, sodium chloride 10% and water-insoluble ingredients, 7% (on the dry basis). Entering into this total of 37% inorganic material are: Calcium, 4.96%; magnesium 2.24%; sodium, 10.52%; potassium, 29.46%; iron and aluminum oxides, 0.43%; chlorine, 34.93%; sulfur (calculated to SO_3), 7.92%; CO_2, 4.44%; phosphorus (calculated to PO_4), 2.30%. All of the kelps contain iodine, though some only a trace.

The iodine content of this species is phenomenal. Of 29 samples analyzed for iodine, an average content of 0.26% was shown, with a maximum of 0.41% and a minimum of 0.17%.

The organic constituents are of a widely varying nature; many of them partake of the nature of sugars. One finds pentosans, galactans, levulans, methyl pentosans and "Alginic" acid.†

Kelps have been shown to be a source also of vitamines. The remarkable vitamine content of certain fish oils, notably codfish

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* Turrentine, "Potash from Kelp" (I-VII). J. Ind. Eng. Chem., Vol. 11 (1919) to Vol. 15 (1923).

† Hoagland and Lieb, "The Complex Carbohydrates and Forms of Sulfur in Marine Algae of the Pacific Coast." J. Biol. Chem. 23, No. 1, Nov., 1915.

oil, has an ultimate origin in the vegetable growths of the sea. The presence of vitamines in various sea plants has been demonstrated by Drummond.

From the foregoing it is evident that kelp contains the principal ingredients of sea water, and has stored them up within itself in even greater concentration than most of them exist in sea water. This is particularly true of potash and of iodine. What other elements are present in kelp likewise present in sea water remains to be shown when specific researches are carried on to demonstrate their presence or absence. It appears logical to assume that practically all of the elements found in sea water are likewise to be found in kelp, since its adsorptive capacity is such as probably to make impossible the exclusion of any one of them. It appears, therefore, to be an ideal concentration of the desirable elements of sea water with the relatively marked elimination of the most common and least valuable—common salt.

Of the fourteen elements above listed as essential to the proper metabolic functions of the human body, thirteen are definitely known to be present in kelp and the fourteenth, fluorine, doubtless will be found when it is looked for.

DESIRABILITY OF KELP AS A DIET AMENDMENT

As a conveyor to the diet of the essential mineral elements, kelp seems to possess many ideal characteristics. Its composition establishes it as a carrier of iodine of remarkable properties —a high content of iodine together with a great assortment of other useful elements. The source of raw material is abundant. Methods have now been perfected whereby the kelp may be so processed that its colloidal parts remain unimpaired and its mineral content unreduced. When so processed it is a carrier of these elements and compounds in a natural, vegetable colloidal suspension, from which or through which they may be taken up by digestive processes just as they would be if they were made available as normal, natural parts or constituents of the usual articles of diet. Being highly concentrated in these, preparations may be made in condensed forms so that transportation costs are reduced to a minimum and the convenience wherewith they may be added to the diet is greatly enhanced. For the latter purpose they may take a variety of forms, suitable for addi-

tion to the diet of people of varying ages and dietary habits. It is important that kelp to be used in connection with goiter be employed as a preventive as well as a cure, that it be added to the diet of the young and to all of those approaching or experiencing life crises. It is contended by some that its addition to the diet should be made a part of a culinary or dietary routine and not left to chance or the caprices of the memory. On the other hand, the disciplinary and educative advantage to be had from consciously taking as a diet amendment a concentrate of mineral matter in tablet form must not be overlooked. Being abundant, cheap and conveniently acquired and stored, it should be made available for all people of all lands. Through its instrumentality, as a carrier of iodine and other desirable elements, not only goiter but any other disease depending on related deficiencies may be eradicated.

The present methods of combatting goiter by the administration of sodium or potassium iodide or thyroxin, leave much to be desired. The administering of iodides, as for example, dissolved in the drinking water of a school, while efficacious in furnishing the iodine requirements of the pupils, results in uneven dosage, though rarely in such an excess dosage as to cause symptoms of iodine excess; yet Bircher* describes the practice as causing harm. Their use should be supplanted by that of iodine carriers which cannot induce idoism.

The administration of thyroxin, the iodine-carrying constituent and an active principle of the secretions of the thyroid gland, is sometimes found efficacious in cases where the gland fails to supply the required amount of that compound. As this is probably only one of the normal products of secretion of that gland if given alone it may not and often does not meet the requirements of the case. Furthermore, to determine the proper dosage it is necessary to know something of the deficiency to be met. So far no technique has been generally adopted for accomplishing this purpose, so the proper dosage is frequently a matter of guess and an overdose may cause symptoms as serious as those it is sought to alleviate. In other words, the use of thyroxin and other thyroid preparations is not based on any thorough understanding of the secretions of the thyroid gland or their functions, nor of the amount required by the system.

* Schweiz. Med. Waschr., **52**, 713 (1922).

What the situation requires is iodine in a form as closely as possible approximating the natural form in which that element is normally taken into the body. Salts of iodine radically fail to meet this requirement. They are very soluble and therefore are able to overcome the natural metabolic balance of the body solutions and thus rapidly force their way into the circulation and out.

Depending on an infrequent administration of iodine salts sets up a feast-or-famine state of affairs and in no sense simulates that constant and steady supply which is the normal method of meeting the body requirements. However, it should be emphasized, this method of combatting goiter is infinitely to be preferred to no effort at all.

It is preferable that the body be permitted to secure its iodine from some natural, vegetable carrier of iodine, by natural digestive processes of selection and elimination through a prolonged digestive period rather than from some chemical, highly soluble and of high penetrative powers, against which the natural protective and defensive agencies of the body are not able to prevail.

Absorption is necessarily different where equilibrium is to be maintained between two absorbing colloids than where a highly soluble salt on the one hand and a colloid on the other are involved. Thus to administer iodine as a suspension in a colloidal, vegetable extract and permit equilibrium to come about between it and the colloids of the digestive system is radically different from the conditions brought about where a highly soluble salt in solution is admitted as one element of the equilibrium.

It must be remembered that iodine is administered in goiter not on account of any physiological action it may have as such, but quite on the contrary. Its physiological action—as exhibited by iodism, for example—is exactly what one desires to avoid. Iodine is given merely to furnish raw material to the thyroid wherewith to manufacture essential secretions. The situation demands physiologically inactive iodine, insofar as such is attainable.

The presence within kelp of other highly soluble halides makes it possible that the chemical and physiological activity of any portion of the iodine present as or converted into iodide

may be "buffered" and depressed. This would tend to function as an automatic protection against an unbalanced dosage and to assist in the maintenance of the proper balance.

CLINICAL RESULTS

Time enough has not yet elapsed since the inception of the idea to use sea plants for the prevention of goiter to make possible a demonstration of the soundness of that proposal. In the therapeutic field, however, very interesting results have been obtained, such, it appears, being obtainable in very short periods of time.

The iodine-carrying constituents of sea plants have been processed into concentrates which, in the form of compressed tablets, have been administered to patients of various ages and victims of thyroid derangement of a variety of forms. Conspicuous among these have been patients who have been kept under constant medical supervision and whose progress has been carefully noted and recorded. Others have had only occasional observation. Without presenting the details of these cases, it may be said the results observed have in the great majority of instances been favorable. The nervous disorders characteristic of hyperthyroidism have responded more readily. "Simple" goiters of long standing and in cases of people of more advanced years have been the slowest to respond.

Among the results observed have been the immediate restoration of the metabolic ratio to the normal and the prompt subsidence of tachycardia and tremor. Cerebral stimulation has become less marked. Hyperplasia has decreased and in instances apparently has entirely disappeared. In the single instance under observation where a serious functional derangement of the ovaries existed, this has been corrected. In all the cases where frequent periods of excitement (violent insanity) occurred,—requiring the confinement of the patient in an institution—these have entirely ceased to appear. In the majority of cases the patient has expressed a marked increase in a sense of comfort, strength, and generally improved health and ability to work without fatigue, and in no instance has there been observed any unfavorable result.

The already considerable and rapidly growing mass of clinical data at hand is not yet sufficient in point of number of cases observed to justify sweeping generalization. At the same

time their positive nature, the number of respects in which improvement has been observed and the advanced stage of some of the cases where benefit has been recorded would appear to justify the belief that the form of iodine and its concomitant mineral elements here used represent a valuable therapeutic agent for use in goiter, particularly where the necessity for an operation does not exist or where the patient is undergoing treatment in preparation for an operation, and probably for the prevention of the recurrence of thyroid derangement following operations.

SURGERY OF THE THYROID

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There are three great questions or problems that confront the medical profession, and laity as well, today. These problems are:

Cancer
Tuberculosis
and
Goiter

Concerning the first, very little is known; as to the second, great strides have been made.

Goiter, the third great problem, is not as complex to the medical profession as the other two, for I believe we have in a great measure found some of the underlying causes of goiter and a successful way of combating it in the early stages before the operation period is reached.

As this meeting is concerned with the study of goiter, I would like to approach it briefly from several angles:

First—Rapid increase of endemic or simple goiter in the United States.

Second—Iodine as a possible prophylaxis.

Third—Fatigue as a cause of goiter.

a. Overwork in adults.

b. Too strenuous exercise in schools, especially among girls.

Fourth—Surgery.

So far the best solution for caring for advanced goiter.

From the best sources of information, we gather that endemic goiter is on the increase in Ohio and other regions that are located in what is known as the goiter belt. Many causes have been advanced in regard to this increase. Chief among these causes as given is fatigue, or overwork. It is therefore important that those who specialize in goiter should investigate all the possible causes and remedies for the condition that is so prevalent in our own locality.

Iodine as a factor in the control of goiter has come into prominence within the last five or six years. The use of iodine as a preventative is not new, for we are told that the Greeks in 2000 B. C. knowingly employed iodine in the treatment of goiter. (Kimball, in American Journal of Public Health, 1923.)

In 1820 Coidet used it as a treatment for goiter, and Bauman in 1895 recognized that the active principle of the thyroid is a very stable compound of iodine. It was proven by Marine and Lenhart that goiter cannot be produced in an animal if the thyroid is kept saturated with iodine; while if an animal is deprived of iodine, the thyroid will start to enlarge as soon as the iodine content gets below one-tenth of one per cent of the total amount of dead gland tissue. (Kimball, in American Journal of Public Health.)

In 1918 work was begun in schools of Zurich. It was found in some schools 100 per cent of children were goiterous. Because of the high incidence of goiter in that region in both sexes the prophylactic treatment was given both boys and girls. The suggestion was accepted that a few milligrams of iodine given weekly throughout the year would produce optimum effects. Instead of sodium iodine the Zurich authorities employed an organic iodid which is non-hygroscopic, almost tasteless and very stable—a vegetable fatty compound which is combined with chocolate and made into tablets—each containing 5 milligrams of iodine.

This method has been employed in St. Gallen, Berne and Zurich for more than three years with even more striking results than those obtained in this country.

This work has also been extended in this country and in at least a dozen cities in Michigan, Ohio and Wisconsin some effort is being made to carry out this work in public schools.

It is possible, therefore, that in endemic goiter districts, if every woman would keep her thyroid saturated with iodine during every pregnancy, she would not develop goiter, nor would there be any tendency toward goiter formation in the thyroid of the child. This would save two of the goiter periods in the life of any individual. If every girl would keep her thyroid saturated with iodine during adolescence—from 11 to 16, inclusive—none would develop goiter. As this work is still in the experimental stage, and as the time covered by these

observations is comparatively short, we must await further results, and in the meantime we should not lose track of other possible causes of goiter, principally focal infections and fatigue.

Turning from preventive treatment of the growth of goiter, I would like to discuss fatigue as a cause of goiter.

In taking the histories and examining a large number of goiter patients it has been impressed upon me that "fatigue" plays an undisputable rôle in the causation of goiter. In almost every instance, the patient with a goiter has undergone a stress in life which has carried her beyond her normal "zone of endurance," whether this stress be mental or physical. For instance, we see goiter commonly in the lower class of farmers, women who have raised large families on meager incomes, teachers and students, especially teachers of the various religious orders, who together with their work have little or no recreation. Frequently we see nurses in training suddenly develop exophthalmic goiter.

The preponderance of goiter in women can be accounted for by a lower point of normal endurance than that found in men. It is a well known fact also that many men develop goiter when suddenly thrown under the stress of army life. Just how fatigue would affect the thyroid it is hard to conjecture, whether it is due to an acidosis, or whether it is a gradually increased call upon the thyroid secretion. I believe that a similar condition exists in the prostate gland which develops in adenoma possibly from over-use. The most logical way of accounting for the formation of an adenoma is a compensatory increase in cells in order to make up an existing deficiency. Every person has a normal zone of endurance which is individualistic in its characteristics. This zone may be decreased or increased by various external or internal conditions; externally by our mode of living, excesses, abuses, atmospheric conditions, hygienic conditions, etc.; internally by gradual toxemia from the intestinal canal, mental strain, focal infection, fevers, etc. The zone may be decreased or increased normally only by changes gradually induced, and has a limit. An example may be the athlete who must train slowly if his endurance is to be increased. The glands of internal secretion act normally, within the zone of endurance; let this zone be exceeded or fall below the normal limit, however, and one

of several changes must take place. If the zone has been exceeded suddenly, then the glands, whichever they may be, are activated to sudden hypersecretion, and if this gland be the thyroid, then hyperthyroidism suddenly develops. I recall the case of a clerk who, desiring an outdoor position, began driving an ice-cream route wagon, which demands heavy lifting and which pays the driver by the percentage of sales, in order to encourage abnormal energy. This man, after two weeks' work, suddenly developed an exophthalmic goiter, which disappeared after his return to his former position. If, on the other hand, the zone has been exceeded gradually, then the changes in the gland are apt to be by a gradual increase of cellular elements and we have an adenoma develop.

Once pathology develops in the thyroid gland, there is a possibility of its tendency being transferred from mother or father to daughter or son. That certain atmospheric, climatic and material differences are more inducive to fatigue than others, would possibly account for the geographic distribution of goiter. I am not aware of the percentage of goiter in the Negro, but I believe it to be comparatively small, possibly because of their lazy dispositions. This is true also of persons residing in the Southern climates. In cases of lung tuberculosis, especially in the ambulatory type, we frequently see signs of hyperthyroidism. When these patients are placed at rest for a while, these symptoms disappear. What probably happens is that the tuberculosis has narrowed the patient's zone of endurance and when she persists in doing the work which she was able to do when well, she exceeds her zone, and the thyroid gland is activated to hypersecretion.

Those of us who have given a great amount of time and study to goiter recognize that an ounce of prevention is worth a pound of cure. But in a large number of the goiter cases that we have to deal with, advanced goiter has developed before consulting a physician or surgeon. For these, surgery seems to offer the only solution.

It has been observed for years past that surgery, with the etiology at hand, offers the most logical treatment for this type of case. Its principal objections, however, have been its immediate mortality rate, its resultant scar, a not infrequent temporary loss of voice, or hoarseness, or an interference with

the singing voice, a resultant myxoedema, or a recurring enlargement of the remaining thyroid tissue and lack of a 100 per cent cure. These objections, which loomed so large a few years back, have, however, been eliminated one by one, until at present the results attending thyroid surgery are equal if not slightly better than the results attending any other type of surgery.

The mortality rate has been gradually reduced, until at present we have a report from the Mayo clinic giving a mortality of less than 2 per cent in over 1,900 consecutive operations, while Crile reports five deaths in 500 operations, a mortality of 1 per cent, and at the same time a consecutive series of 331 thyroidectomies and 145 ligations with no deaths.

In our own series of 1,245 thyroidectomies and 253 ligations, or 1,498 cases in all, we have had 21 deaths, a mortality rate of approximately 1½ per cent. In this series only a few cases were refused operation, many of which were "in extremis" when they entered the hospital. We have classed as operative deaths all cases which died while at the hospital. Fifteen of these deaths were following bilateral resections, 5 were following unilateral resections, and 1 following simple single ligation. Of the bilateral resections which died, two died within forty-eight hours from acute hyperthyroidism, and one on the ninth day from myocardial insufficiency, the reaction following operation having been comparatively slight. Of the 5 deaths following unilateral lobectomy, one died two hours following operation; the exact cause was never determined, although collapse of the trachea was suspected; another died seven days following operation from cardio-renal insufficiency. This patient had lost fifty pounds within three months preceding operation. Two ligations had preceded his lobectomy. Since this death I have placed a bad prognosis upon every thyroid case presenting a rapid loss of weight. The death which occurred following single ligation was due to acute hyperthyroidism, death occurring on the third day following. In other words, counting only immediate operative deaths, our mortality would figure about 1 per cent. In the last 500 cases, we have not had a death from acute hyperthyroidism, due largely to improved judgment.

The resultant scar is scarcely noticeable and frequently

imperceptible when the incision is properly placed and properly closed. The incision which we use now is in the lower crease of the neck, about one-half inch above the sternum. We have found that because of the looseness of the skin of the neck this incision gives a better and less noticeable scar than when placed in a lower position. We close the incision by placing a very fine catgut suture in the platysma and use small skin-clips for the skin. We remove these clips on the third day following operation, or approximately seventy-two hours. We use a small strip of gauze saturated with vaseline, which is brought out in the center of the wound, and leave the drainage in place for 24 hours. We have found that even when an infection results it can be satisfactorily handled through this opening without separating the incision. If the infection becomes alarming, however, which is very rare, then the incision may be opened.

Temporary loss of voice or hoarseness is not an uncommon sequel of thyroid operations, but concerns us chiefly because of the temporary discomfort. Permanent aphonia has only been reported in the literature as occurring twice. In one of our patients the voice entirely disappeared for four months, then gradually returned to normal. In six the voice was reduced to a whisper for three to five months, then gradually returned to normal. In 5 per cent of all bilateral resections a tracheitis and laryngitis resulted, many of which persisted for four to six weeks. Lately we have discontinued stripping the entire isthmus from the trachea, but are leaving a small strip of gland overlying and the inflammation following has neither been so severe nor so frequent. Interference with the voice following operation is frequently due to a combined laryngitis and tracheitis rather than to injury to the recurrent nerves. Another technical point which may be mentioned in order to avoid injury to the nerves is to wipe the capsule away from the gland with gauze dissection, thereby carrying the nerves away from the field of operation. Resultant attachment of the scar to the trachea not infrequently interferes with the singing voice. To avoid this we divide the sternothyroid and hyoid muscles at least one inch above the skin incision.

Evidence of myxoedema following bilateral resection oc-occurred in only three or four cases, and this was immediately and permanently relieved by a two months' course of thyroid

extract, together with our routine post-operative régime, dependent upon the cause, of which we speak later.

Recurring enlargement of the remaining tissue is apt to occur, especially following bilateral resections for colloid goiter. This speaks for, and evidently is, a compensatory recurrence. Crile gives iodine in these cases, basing its administration upon the control of endemic goiter with iodine; but we go farther and attempt to eliminate the cause of the original enlargement whenever possible. We have found that this type of goiter especially is prone to follow any elements which tend to exceed our normal zone of endurance.

Surgery's chief criticism in thyroid surgery has resulted because we occasionally find cases which are not benefited; in other words, surgery is not a 100 per cent cure in thyrotoxicosis. This is so, I believe, because surgery, up to the present, has not been founded upon a definite etiology. In order to effect a complete cure, therefore, it is not sufficient to merely remove the pathology, but we must also in our post-operative treatment attempt to eliminate the primary cause of the pathology. And this is true in other surgery as well. With this in view, we have attempted to establish a post-operative régime, whenever possible, which will tend to prevent a recurrence of the goiter or its symptoms and thereby affect a cure.

The discussion of the various phases of the etiology of goiter which we have given lends itself admirably to a logical post-operative régime, keeping the patient well within her "normal zone of endurance," insisting upon a certain amount of relaxation and recreation, changing occupation when thought advisable, overcoming constipation, etc.

With the above surgical interference and post-operative régime, we have estimated an improvement in all cases, consistent with a normal endurance in fully 90 per cent of cases.

DIAGNOSTIC ENDOCRINE CLINIC

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The immense amount of rich material that has been collected for this clinic is a marked complement to the program committee of this Association. More than twenty interesting and rare endocrine disorders have presented themselves for diagnosis. Of this number only thirteen were selected, and in order to economize your time these have been arranged for demonstration in groups.

The fact that so much material could be accumulated so easily and quickly demonstrates two very important facts concerning the necessity of more intensive study not only of the thyroid, but of the ductless gland disorders in general. The first and most important fact is that these internal seretory diseases are so common that their incidence is as marked as diseases of any other system. Second, there is a great demand and a very pressing need for every stimulus that can be brought to bear upon the study of and research in the disorders of the ductless glands. It is just here that this Association, which really should be a part of the International Association for the Study of Internal Secretions, has its most purposeful field. For many years we have been educated through the work of the surgeon in the anomalous functions of the thyroid. With the exception of this *one* gland, however, I believe that the real importance and prevalence of endocrine disorders are not appreciated. In order to demonstrate the frequency of ductless gland disorders as compared with diseases of other systems of the body, it will be necessary for me to quote from personal experience. In conducting a practice of internal medicine which is not limited to any particular field (for we believe that it would be ridiculous to attempt to make a specialty of the internal secretions), we have found, during the last five years, that there were as many disorders of the ductless glands presenting themselves for diagnosis at an internal medicine clinic as there were diseases of any other one system. That is, there are actually

as many endocrine disorders as there are lesions of the cardiovascular system, the respiratory system, the gastro-intestinal system, the genito-urinary system, or the muscle-osseous system. We are sure that this prevalence of internal secretory disorders is not limited to one section of the Middle West. On the contrary, the condition prevails to a greater or lesser degree throughout the entire country. Yet it is difficult to impress this fact upon the medical profession, who believe (1) that the ductless gland disorders are very rare, (2) that they are very difficult to diagnose, and (3) that when an occasional case is diagnosed the treatment is of little avail. This medical idea exists, I am sure, because of the lack of knowledge concerning the endocrines in general, and this lack of knowledge is due to the fact that there has been very little taught in the medical schools of this country on ductless gland disorders. There are only two universities in the United States which give systematized courses in internal secretions, the University of Pennsylvania, which has dedicated a department in honor of Professor C. E. de M. Sajous, and the St. Louis University School of Medicine.

This is a field which should be presented more directly to the layman on account of the fact that it deals with the basic principles of growth and development of the individual. Particularly necessary is the knowledge of these important functions during the early life, when the internal secretions have such an influence in developing the nervous system. We have had public campaigns of education on other diseases, such as syphilis, tuberculosis, cancer, and venereal disease, all of which pertain to acquired diseases of the adult,—in many cases late adult life, for which the patient is personally responsible after he has arrived at a mature age when he should be independent and able to exercise the ordinary precautions against advanced and unfavorable conditions resulting from neglected early treatment. The endocrine disorders, however, affecting the helpless infant and dependent child, producing such marked retardation in the infantile and juvenile growth and development, with subsequent mental incompetency and delinquency, have been neglected entirely. The medical profession as well as the laymen have indifferently and inactively allowed thousands of children to pass through this abnormal stage of maldevelopment and immature growth into an incompetent, defective or criminal.

For this reason every city and state of the Union have on their hands in almshouses, sanitariums, and asylums hundreds of thousands of these individuals, who become a tremendous charge upon the state, as well as tragic afflictions to their families and relatives.

As has been stated before, there has been an unusual amount of work done upon thyroid disorders, but ninety per cent of this has been devoted to the hypersecretion of the thyroid. There has been comparatively little advanced in the *early diagnosis and treatment of hypothyroidism*, and until recently an insignificant amount of work has been devoted to the *other glands of internal secretion*. Yet when we begin to study these subjects intensively, we are surprised to discover that there are as many pituitary and gonadal disorders as there are thyroid disorders, and probably if more were known about disorders of the adrenals, thymus, and other glands, we should be startled to discover that they also are as prevalent as the thyroid disorders. For this reason, while this Association is devoting its efforts entirely to the study of goiter, I believe it will serve a good purpose, because no one can earnestly take up the study of one of these glands without becoming intensely fascinated by and carried along to the study of the interrelationships of the ductless glands.

GROUP I, BILOBAR INSUFFICIENCY OF THE HYPOPHYSIS

Owing to the large material we have to demonstrate in a short time, it will be necessary to speak only of the general diagnostic signs which can be objectively shown. Neighborhood signs or special studies devoted to the basal metabolism, blood chemistry, etc., cannot be given consideration in these cases. After all, it is the general hormonic signs presenting themselves so objectively which are the most important diagnostic signs. A suspect diagnosis can be made in many of these cases from a rather casual examination and cursory history.

In the first group we will show three cases of juvenile adiposity, which is one of the early classical signs of insufficiency of the posterior lobe of the pituitary gland in the preadolescent age. It can be seen that all these children are very much overweight, without taking time to weigh them or compare their weights with the standard for age and height. For instance, Case No. 1

is a boy aged thirteen weighing over 160 lbs.; Case No. 2 a girl aged ten weighing 205 lbs.; and Case No. 3, a male aged fourteen weighing 230 lbs. It might be well to stop just long enough to discuss adiposity in general at this time. Our monograph on "Endocrine Adiposity" appearing in the Clinics of North America, St. Louis Number, Vol. 6, No. 1, 1922, gave our ideas with regard to the diagnostic value of the age incidence of adiposity. In this article we stated that (1) an adiposity occurring at birth (a weight of over 8 lbs.) means in seventy per cent of the cases, excluding birth anomalies, moronism, and mongolism, a hypothyroidism; (2) and adiposity occurring at the juvenile age indicates in eighty per cent of the cases insufficiency of the posterior lobe of the pituitary gland, usually associated with insufficiency of the anterior lobe; (3) an adiposity occurring in late adult life may be due to single or combined hypothyroidism hypopituitarism, or hypogonadism; and (4) an adiposity occurring in the juvenile or early adult life, however, could never be attributed to hypogonadism or hypothyroidism. In the same article we give other points for differentiating these adiposities, such as the distribution of the panniculus, associated endocrine signs, and the effects of therapy. There is, however, a great deal of contention regarding the etiology of adiposity. Professor Arthur Biedl, of Prague, is much inclined to attribute these obesities to a cerebral or hippocampal lesion. B. A. Houssay, of Buenos Aires, is more inclined to believe that he has proven experimentally that the lesion is located in the interpeduncular neighborhood of the pituitary gland, but not in the hypophysis itself. Aschner, of Switzerland, claims that lesions of the tuber cinereum have produced this classical type of adiposity in animals. Bremer, of Antwerp, and Bailey, of Boston, also are inclined to attribute these obesities, as well as other so-called hypophyseal signs, to extra-pituitary lesions of the hippocampal region. The French school, led by Camus and Roussy have maintained for many years that lesion of the hypophysis does not account for this type of adiposity nor for some of the other symptomatology attributed to the pituitary gland, and relate them to perihypophyseal lesions. Professor Julius Bauer, of Vienna, gives to the primary inherent gamete and zygote cells the property produced by chromosomal deficiency, the etiological factor in the production of adiposity. He claims that if the indi-

vidual cells producing this panniculus were dissected off one portion of the body, the hips, for instance, in the pituitary case, and engrafted upon the back of hand or the supraclavicular region, they would continue with the overgrowth and production of the adiposity.

Contrary to all this contention and, for the most part, physiological proof in animals, we have continued to believe that the majority of these juvenile obesities are due to internal secretory disturbance and that the adiposity in these particular cases is caused by deficiency of the posterior lobe of the pituitary gland. It cannot be disproved, however, that the function of this portion of the gland may not be influenced by lesions or nervous impulses coming from various portions of the brain, hippocampal gyrus interpeduncular region, tuber cinereum, etc. This boy (Case No. 1) does not show as decided an insufficiency of the hypophysis as the other two cases (Nos. 2 and 3), yet the adiposity is evident in ordinary street clothes and is very classical in its distribution. Besides the adiposity he has the characteristic small head, hands, and feet in comparison with the rest of the body. With the classical pituitary adiposity, limited to the girdle region, particularly the hip and shoulder girdles, the lateral aspects of the chest, and the lower portion of the abdomen, he has the mammary adiposity, which, occurring in the preadult age (in his case at thirteen) or in late adult life, indicates gonad insufficiency. For this reason we would suspect that he has a primary insufficiency of the *anterior lobe* pituitary gland, because we know that when the anterior lobe of the pituitary gland does not function sufficiently, it indicates that the gonads (testicles, in the male) will not develop properly. In these cases we would expect an absence of development of the generative organs during the age of adolescence. This, after all, is the most important circumstance to suspect and *prevent,* if possible, in these cases. It is well known that if in either sex there is an imperfect development of the generative organs at the adolescent age, there will be a very decided change in the psychic state, as well as in the future physical growth, of the individual. This maldevelopment will tend to prevent the proper contact and association of these individuals, with the consequent interference with their projection in social and business life. Whether or not we can predict the genital development of this case in the next

year or two cannot be determined by mere physical examination, but the fact that he has an abnormal mammary and mons adiposity would lead us to suspect very strongly that this system will be hypoplastic. Until recently, however, we had no other means of estimating the function of the anterior lobe before the preadolescent age, when the genitals should normally develop. Now, however, by studying the osseous development, X-raying certain bones for each yearly age to dêtermine whether the nuclei of certain epiphyseal ends have appeared or united with their shafts, we can determine rather definitely whether the anterior lobe of the pituitary gland is performing its normal function. This lobe influences the growth and development of the osseous system during the preadolescent age, besides exerting its influence upon the growth, development, and function of the genital organs at adolescence. Knowing the development of the osseous system in the normal, as shown by the X-ray, and comparing this normal development with that of a case under investigation, allows us to determine the function of the anterior lobe a number of years preceding adolescence. (See "Osseous Development in Endocrine Distorders," Engelbach and McMahon, Endocrinology,, Vol. 8, No. 1, January, 1924.) This is most important from the standpoint of treatment, because it is known that unless these cases are *diagnosed a number of years previous to adolescence and treated intensively at that time,* the most opportune age epoch for the stimulation of the growth and development of the genitals is passed.

Case No. 2 is a girl ten years old weighing 205 pounds. The history in this case is that of an adiposity which began early in life, at just what age cannot be determined, and gradually increased to the present time. She has the same distribution of panniculus as the boy (Case No. 1). The obesity in the mammary region is very abnormal for the age of ten, which would indicate that the anterior lobe of the pituitary gland is more or less functionless and consequently that she will not mature properly when she arrives at the age of fourteen. We would suspect that she is doomed to more or less imperfection of her menses, varying from irregular, scanty periods to a possible complete amenorrhea, associated with frigidity and sterility. The adiposity across the hips observed in this case is what we call the classical girdle adiposity, so characteristic

of posterior lobe pituitary insufficiency. The distribution of the adiposity, as you know, in various ductless gland disorders is entirely different. In the posterior lobe insufficiency of the pituitary gland we have the adiposity distributed particularly in the girdle region, involving mostly the inferior or hip girdle, with slight increase in the shoulder girdle. In the thyroid insufficiency the adiposity is characteristically located at the dorsum of the wrist and the supraclavicular region, but there is also a tendency to a more or less even, diffuse distribution of adiposity, extending down over the dorsum of the arch of the foot. In insufficiency of the gonads (generative organs) the adiposity is located particularly in the mammary suprapubic and trochanteric regions. In those cases having two or sometimes three ductless glands insufficient we have more or less fusing of the various areas of panniculus, or an engrafting of one type of adiposity upon another. For instance, in the pituitary insufficiency involving both the anterior and posterior lobes we really have an adiposity due to the posterior lobe of the pituitary gland, consisting of a girdle adiposity combined with a gonadal adiposity due to a primary insufficiency of the anterior lobe pituitary gland, which has caused a secondary decrease of function of the gonads and a consequent deposition of panniculus in the mammary glands in the trochanter region, and on the mons. The important fact we wish to emphasize is that this girl probably will not mature correctly when she reaches the adolescent age. This will produce a great many secondary symptoms referable to her nervous, cardiovascular, and gastro-intestinal systems. Many such cases are treated as primary lesions of these systems, whereas the actual cause of the condition is the lack of ovarian function, which is primarily due to an insufficiency of the anterior lobe of the pituitary gland. *For this reason we have tried to emphasize the fact that juvenile adiposity is really the danger signal that indicates the probability of lack of genital growth and function,* with its consequence in the postadolescent age. In addition to this secondary gonad insufficiency due to anterior lobe pituitary deficiency there is added to the majority of these cases which have had a bilobar pituitary insufficiency for a number of years an insufficiency of the thyroid gland, which complicates the condition very considerably and adds untold difficulties to its re-

lief by treatment. In these conditions where we have a thyroid insufficiency added to a primary pituitary insufficiency we do *not* get an abnormal metabolic rate, which has misled a great many observers. Our experience in routinely examining about 2,500 endocrine disorders, 875 of which were pluriglandular, has led us to believe that the basal metabolic rate is not a guide to the function of the thyroid gland in pluriglandular disorders. This rate might be within the normal and yet the thyroid gland may be either very much increased or decreased in its function. While we have a great deal of confidence in the basal metabolic rate as a measure of thyroid function in simple uniglandular thyroid disorder, it is our opinion that the above statement maintains in all those conditions in which the thyroid disorder is only a part of a pluriglandular dyscrasia. We have proven this to our own satisfaction in obtaining remarkable therapeutic response to thyroid substitution in these pluriglandular disorders having a normal or even metabolic rate.

This introduces the subject of polypharymacy in the treatment of ductless gland disorders, i. e., *whether or not we should give a combination of various ductless gland substances in suspect* pluriglandular insufficiency. As a rule, we believe this method of pluriglandular therapy is very poor practice. It should not be attempted until one has had a great deal of experience in clinical endocrinology and has become quite expert in the exact diagnosis of pluriglandular disorders. We will progress more rapidly in both diagnosis and treatment if we give one ductless gland preparation at a time, and by watching the therapeutic reaction of this substance, determine whether or not the patient has a deficiency of a single gland. In a given case which might be diagnosed, for instance, as thyro-pituitary (bilobar) deficiency, that is, insufficiency of the thyroid with both lobes of the pituitary gland, we would first substitute thyroid substance to tolerance, giving the desiccated gland, until the patient begins to have some signs of thyroid intoxication, and closely observe the effect upon the general symptomatology, such as the mental state, adiposity, changes of the skin and its appendages, and of other systems, as the cardiovasculorenal, etc. If the patient does not react to this satisfactorily, we would then withdraw the thyroid treatment and give pituitary treatment, using the substance from one lobe at a time, say the pos-

terior lobe. If this is not productive of the proper therapeutic response, we would then give anterior lobe substance, and if this is followed by no favorable reaction, a combination of the anterior and posterior lobe substances may be given, and possibly later the anterior and posterior lobe and thyroid preparations. The most convincing knowledge in both diagnosis and treatment of ductless gland diseases as has been said before, has been obtained in this way from observing the therapeutic response in suspect endocrines.

Case No. 3, a boy aged fourteen, has an obesity so striking that it is unnecessary again to call your attention to its girdle, mammary, and mons location. It is a sad implication on the medical profession that this outstanding sign, so easily recognized, is not taken for its face value as indicating probable pituitary deficiency. If recognized and treated in the early juvenile age the results are comparatively good with simple treatment; whereas, if it is neglected for a number of years, during which time there is a probability that the anterior lobe also has become underfunctionating, the reaction to treatment becomes less and less marked. We have realized that the *early diagnosis in these disorders* is very much more important than the early diagnosis in diseases of other systems, not only on account of the greater ease with which results are obtained from treatment, but, in addition, because the *disorder of other ductless glands* produced by the primary uniglandular disorder *is frequently prevented.* You will note in this case the same mammary adiposity present in the other two cases. On examining the testicles we find that they are about the size of a pea, and the penis is about the length of the terminal phalanx of the little finger. This hypoplasia of the genitalia, taken with the mammary adiposity at this age (fourteen) indicates that there is, in addition to the posterior lobe insufficiency, an insufficiency of the anterior lobe, and that it is probable that the genitalia will remain in an aplastic state as far as growth and development are concerned and consequently may have no function. Besides having a marked physical defect, such as the unusual adiposity and the underdevelopment of the genitalia, these individuals are social outcasts, having no generative function and consequently being denied the privileges of the marital and procreative states. The diagnosis made at the age of four-

teen in these cases, as stated before, is too late to produce the best therapeutic results. It should be made in the great majority of these cases many years before, when the adiposity begins to develop and the individual is overweight for his height and age. Treatment instituted at that time should prevent this enormous adiposity and the atrophy or tendency to hypoplasia of the generative organs.

Case No. 4 is a girl thirteen years old, weighing 230 pounds, who gives the following history: Her weight at birth was 7½ pounds, her teeth came in early, she walked before one year of age, and talked before the age of one, indicating that there was no possibility of her having had a congenital hypothyroidism. She has complained more or less of migraine and ocular symptoms during her childhood. Her mental development and progress through school have been normal. Her adiposity began about the tenth year and has increased very rapidly to the present age (weight now, at the age of thirteen, 230 pounds). She had one period 6 months ago, since which time she has had an amenorrhea. It is unnecessary to go into detail again regarding her adiposity, which conforms to the type demonstrated in the previous cases, but I wish to call your attention to the menstrual history, which is very characteristic in these cases, being analogous to the undergrowth and underfunction of the genitals demonstrated in the boy, Case No. 3. This girl had one period six months ago, since which she has had no periods or signs of menstrual activity. This is a very frequent occurrence in these cases, indicating the insufficiency of the anterior lobe of the pituitary gland, whose hormone is one of the regulating factors in the growth, development, and function of the genital system, as well as in the growth of the osseous system. Many of these cases do not have periods at all. We have now collected quite a series of women who have a primary anterior lobe pituitary insufficiency, of various ages, from fifteen to forty, with complete amenorrhea, the genital organs remaining infantile with regard to development, with complete absence of function. Besides longer or shorter periods of amenorrhea present in these cases, other aberrant forms of anterior lobe insufficiency have various types of menstrual imperfection, such as marked dysmenorrhea, metrorrhagia, and various combinations of these menstrual disorders. After all,

the hypoplasia of the genital organs is very much more important than the deformity caused by the adiposity subsequent to the insufficiency of the posterior lobe of this gland. The adiposity, at least, does not produce very marked changes, reflex or hormonic, in other systems; whereas an imperfect generative organ function disturbs the economy of the whole body, including the important functions of the cardiovascular, nervous, and gastro-intestinal systems.

Before dismissing this case as well as the others in this group, we wish to call your attention to the fact that in none of the simple pituitary deficiencies involving both lobes of the gland is there a defect of the mentality, so prominent in the cerebral adiposities and pure thyroid insufficiencies, some of which will be demonstrated in the next group. This mental state in itself serves to differentiate severe thyroidism from simple pituitarianism and also helps to determine whether or not the thyroid is involved with a pituitary insufficiency.

GROUP II, THYRO-PITUITARY (POSTERIOR LOBE) INSUFFICIENCY

This group consists of three cases of insufficiency of the thyroid gland which was present at birth (congenital hypothyroidism), to which was added later in the early juvenile life insufficiency of the *posterior lobe* of the pituitary gland. Before taking up these cases individually I wish to discuss the early signs of hypothyroidism, which should be known by every layman, as well as physician. These concern the signs presented from birth up to the first year of life, indicating normal or abnormal development, such as the weight at birth, the time of eruption of the first tooth, the time of walking and of talking. First, a normal baby would not weigh more than 8 pounds. An infant who does weigh more than 8 pounds at birth should be suspected of having a hypothyroidism. This would be the correct diagnosis in seventy per cent of the cases. With the exception of birth anomalies, such as hydrocephalus, monsters, etc., which can be excluded by inspection, the other thirty per cent of those overweight at birth usually turn out to be morons or mongols. A few babies who are overweight at birth do not develop later into abnormal children. Ninety per cent of the children giving histories of cretinism and positive hypothyroidism in later life, however, give histories of overweight at

birth, in addition to the other three cardinal signs. Second, the first teeth should be erupted not later than seven months, and all children who have been overweight at birth and do not have the first tooth at seven months should be suspected as probable hypothyroidisms. Third, a normal child should walk at the age of one year, and fourth, he should begin to put words together at the age of one year. If all these four cardinal signs are positive, further confirmation may be had with regard to the diagnosis of hypothyroidism by X-raying the hand, knee, and foot. At birth, the nuclei for the lower end of the femur and two tarsal bones (talus and calcaneus), should be present. At the end of one year there should be present two nuclei for the carpals (hamate and capitate), the distal epiphysis of the femur, the proximal epiphysis of the tibia, and those for three tarsal bones (talus, cuboid, and calcaneous). Dr. Alphonse McMahon and I have compared the development of the entire osseous system in the normal with the osseous development in various types of endocrines as shown X-rayically, in the Journal of Endocrinology, Vol. 8, No. 1, January, 1924. These studies are particularly valuable in the early diagnosis of hypothyroidism, the preadolescent diagnosis of anterior lobe pituitary gland insufficiency, and the diagnosis of hypogonadism in early adult life. When we realize the apparent poor results that have been obtained in the treatment of cretinism, we begin to appreciate the necessity of very early diagnosis, and by early diagnosis we mean in the first year of life, instead of at five or six years of age, the average duration of these cases today before treatment is instituted. The demand for thyroid hormone is so great during the first few years of life, when the entire nervous system, as well as the various other systems, normally is developing so rapidly that, unless the thyroid gland is properly functioning at this time, there is a retardation of growth and development in these systems which cannot be overcome, even if treatment is started in the juvenile age.

These three children belong to the same family. Case No. 5 is a boy six and one-half years of age, who weighed 8 pounds at birth. Case No. 6 is a girl four and one-half years of age, who weighed at birth 8½ pounds. Case No. 7, two and one-half years old, weighed at birth 8 pounds. The weight at birth of these three children should make the doctor suspicious at once.

He should at least inquire very carefully with regard to the future development of these children. Case No. 5 walked at ten months and talked at three years. Case No. 6 walked at fifteen months and started talking at four and one-half years. Case No. 7 walked at one year and is just beginning to talk (at two and one-half years). All, by the way, had poldactylism, Case No. 5 having had three extra fingers, Case No. 6 two extra fingers and one toe, and Case No. 7 one extra finger. We know the mental retardation in these children cannot be due to pituitarism, as has been stated in the discussion of pituitarism in the previous group. We also know that the adiposity in these children cannot be due to thyroidism, because we know that thyroidism does not produce an adiposity after the first one and one-half or two years. From the histories alone we can say that all three had more or less thyroid insufficiency at birth and during the first year of life. To this, however, has been added later in the lives of these children an insufficiency of the posterior lobe of the pituitary gland. This combination of thyro-pituitarism has been impressed upon us during our investigations in the last four or five years, and I believe it is one of the reasons for not obtaining better results in the treatment of these cases, for the majority of these children are treated as cretins and not as primary cretinism to which has been added a pituitarism. The pituitary insufficiency is given no consideration in the diagnosis or treatment. The diagnosis in these cases, on the contrary, has been considered so difficult that most physicians do not profess to be able to make it. Yet you see after all that the diagnosis is made upon such simple facts as the history of the first year of life and the advent of the adiposity, and it is just this gross objective sign and easily obtained information which we believe the most important diagnostic evidence in these cases.

GROUP III, THYRO-PITUITARY (ANTERIOR LOBE) INSUFFICIENCY

This is another group of thyro-pituitary insufficiency in which there was a congenital deficiency of the thyroid gland, to which later in life was added an insufficiency of the *anterior lobe* of the pituitary gland, without an involvement of the posterior lobe. Case No. 8 is a boy aged eleven, and Case No. 9 a girl aged nine, brother and sister. The girl is almost as tall

as the boy. Both have marked retardation in growth and some retardation in mentality. The early histories are as follows: The girl weighed 8¼ pounds at birth, the first tooth appeared at the age of ten months, she walked at fourteen months, and did not talk until fifteen months. The boy weighed 9½ pounds at birth, his first tooth appeared at six months, he walked at fourteen months, and could not understand much that was said at two years. You will note that the chronological history in each case indicates the abnormal development which is so common in hypothyroidism, but instead of becoming obese later in life (as did Cases Nos. 5, 6 and 7), both these children have remained rather frail and undeveloped. In fact, it was this undernourishment and inability to gain weight which induced the parents to seek medical aid. Notice that neither has the adiposity that is present in the previous groups of pituitarism, either those complicated (Nos. 5, 6, and 7), or those uncomplicated (Nos. 1, 2, 3, and 4), by thyroidism. Besides this there is a very marked retardation in growth in these cases, that was not present in the thyro-pituitary individuals of the previous group (Nos. 5, 6, and 7), having the posterior lobe pituitary involved instead of the anterior lobe, as present in these two cases. We have noted for a considerable number of years that some cretins have remained unusually small and emaciated and free from adiposity, while others, who apparently were just as characteristic cretins from their first year history and mental retardation, have taken on an unusual amount of adiposity, and it was not until the last three or four years that we were able to explain the so-called emaciated cretin, as well as the obese cretin. When we compare this type with hypothyroidism in the adult we see that there is a similar type in the later ages. For instance, in the typical myxedema, which has been so well described by Sir Wm. Gull and Wm. Ord, we have a classical adiposity associated with the hypothyroidism; whereas in the "cachexia pachydermique" of Charcot of the "cachexia strumipriva" of Kocher we have a very marked cachexia following a complete removal of the thyroid. In the congenital thyro-pituitary (anterior lobe) deficiencies we have a very much more marked retardation of the osseous growth than in either simple thyroid or anterior lobe pituitary insufficiency.

The treatment in these cases of thyro-pituitary (anterior

lobe) deficiency, of course, is entirely different from that directed toward the simple thyroid or the thyro-pituitary (posterior lobe) insufficiency. In these cases an attempt should be made to substitute not only the thyroid deficiency, but also the deficiency of the anterior lobe pituitary gland; whereas in the thyroid and posterior lobe insufficiencies the treatment should be directed toward overcoming the decreased function of the thyroid gland, as well as that of the posterior lobe pituitary gland. It is very rarely noted that the cases have ever received more than simple thyroid substitution, and in most of these cases this treatment has not been instituted until after the thyroid, as well as the pituitary gland, had been functionless for a number of years, the body as a whole during this time having suffered the lack of both of these important hormones in its growth and development. In order to get the best results it is necessary not only to make the diagnosis in the first year of life, but also to give sufficient treatment at this time to overcome the thyroid deficiency, and this probably in itself would prevent the additional pituitary disorder which seems to be the logical sequence in untreated or insufficiently treated thyroid deficiencies. However, when the pituitary gland is already involved, the treatment must be directed toward its underfunction as well as the thyroid deficiency, taking into consideration the amount and duration of the disorder present, in order to accomplish as much as possible.

GROUP IV, THYROID INSUFFICIENCY

DEMONSTRATING IMPROVEMENT FOLLOWING EARLY DIAGNOSIS AND TREATMENT

Case No. 10 illustrates the effect of treatment in a case of thyroid insufficiency in which the diagnosis was made by Dr. E. P. Sloan of Bloomington, at the age of one year and treatment was given intensively at and subsequent to that time. This boy is now aged twelve. He weighed 11¾ pounds at birth, his first tooth erupted at seventeen months, and he began to put words together at two years. Very early in the first year of life he began to have gastro-intestinal disturbances which were very pronounced. At the age of one year he first began to take thyroid treatment, after which the gastro-intestinal disturbances, such as nausea and vomiting, undernourishment, diar-

rhea, etc., improved very quickly and soon disappeared. This is another very important and common occurrence in hypothyroidism. The pediatricians have a great deal of trouble adapting a food to these children. They say they are very peculiar babies who do not accept the ordinary milk mixtures and for this reason are usually very much undernourished and have a great deal of trouble with their feeding during the first year of life. This boy (now twelve years of age) has been taking thyroid treatment ever since he was one year old. You will note that he is fairly well developed. He has some mental retardation, as shown by the history that he has some difficulty in school, but this is not marked enough to put him behind his classes. There is no question but that the early diagnosis and treatment has saved him from a complete mental as well as physical, deficiency. The question arises now whether he has not drifted into a partial insufficiency of some other ductless gland, in addition to his hypothyroidism. We would suspect that probably there is some anterior lobe deficiency in this case, in addition to the hypothyroidism. We feel sure that he has no posterior lobe involvement, on account of the absence of classical obesity which exists with deficiency of this lobe of the pituitary. In order to determine this it would be well to X-ray the bones for the ages of twelve (the elbow and carpals). In addition it would be well to X-ray the bones for the ages of eleven and thirteen. All these are given, with comparative tables and X-ray pictures for the normals and abnormals of the same ages, in the article on "Osseous Development in Endocrine Disorders" (Endocrinology, Vol. 8, No. 1, January, 1924). In the X-ray osseous studies of the endocrines we were very much surprised to find that the thyropituitary osseous development was advanced with regard to the appearance of the ossifying nuclei of the various bones for the age of the individual, whereas in the simple thyroidism, without a pituitary complication, there was a remarkable retardation in the appearance of the osseous nuclei as compared with the normal for the age. We feel that this is a very important diagnostic point, helping us to determine whether in a given suspect pluriglandular disorder having a definite thyroid involvement there is a complicating pituitary or gonadal element, which sometimes is

rather difficult of determination from the history and physical signs alone.

GROUP V, PLURIGLANDULAR INSUFFICIENCY, WITH EPILEPSY

Case No. 11 is a boy whose chief complaint is epilepsy. He has a very definite endocrine makeup, as will be seen from the various ductless gland signs, as follows: The orthodontial signs are marked in this case with very marked malocclusion of the teeth, some teeth being twisted almost half around in their sockets. The eyes show internal strabismus, which brings up another rather important point relating to the internal secretions. It is known that the eyeball accommodates itself to the bony socket containing it. The growth of the bones is under the influence to a large extent of the internal secretions. The anterior lobe pituitary, thyroid, thymus, and gonads particularly influence the growth and development of the various bones. When the bones do not grow properly the eye socket does not obtain its proper shape, consequently the eye is either too long or too short. This deviation from the normal in its axis prevents the rays of light from falling upon the retina in the normal way, and in order to overcome this error of refraction the ciliary muscles of the lens are put to a strain, and it is this strain which causes the infant to throw one eye past the normal meridian, producing strabismus or the so-called cross-eyed condition. This illustrates how the internal secretions dovetail themselves into almost every specialty, and no matter what fields of medicine we are practicing, we cannot afford to be without the information obtained in the study of this subject. The next meeting of the American Otolaryngological Association, to be held in St. Louis, is to devote the entire session to the study of the internal secretions as related to diseases of the nose and throat. This boy demonstrates the relationship of the internal secretions to the eyes and to the teeth, as well as to the mental makeup or nervous system, as shown by his epilepsy. Another important factor in his history is that these attacks of epilepsy stopped almost entirely during two months following the influenza, illustrating the effects of infections upon the functions of the ductless glands. We know that a great many disorders of the ductless glands follow simple infections, such as measles, whooping cough, diphtheria, influenza, typhoid fever, etc. Typhoid toxin particularly seems to

have a decided effect upon pituitary function. Influenza toxin probably has a more decided effect upon the adrenals, as exhibited by the prolonged malaise and extreme mental and physical fatigue following a severe attack of influenza. The general makeup and status of the osseous growth and the genital development in this patient go to speak for endocrine disorder. Examinations by two very good neurologists have failed to demonstrate any focal or local nervous lesion accountable for his epilepsy. The one ductless gland disorder with which epilepsy is most frequently associated is the pituitary, producing uncinate epilepsy, as it is now called. These epileptic attacks due to pituitary disease are usually preceded by disturbances of either the gustatory or the olfactory sense. That is, the patient during the aura or when recovering from the epileptic convulsion has a very marked perversion of the sense of smell or taste. If such a characteristic attack occurs having these peculiar gustatory or olfactory associations, that can be relieved by pituitary treatment, then we believe one is justified in saying that it is a case of pituitary epilepsy. We also have a peculiar attack of epilepsy in young children due to thymus disease, which is very easily relieved by X-ray of the thymus. We have had a number of cases of this kind having very severe epileptic convulsions, as frequently as two or three times a day for over a year, that we have relieved by one or two X-ray exposures of the thymus, completely and permanently for one and one-half to two years.

Epilepsy also occurs in a comparatively few cases of thyroid insufficiency, as has been proven by complete relief of the condition for a period of over five years by simple thyroid medication. As a whole, however, the percentage of endocrine epilepsy is small compared with the total number. We would say that not more than two per cent of the epilepsy have their etiology in the endocrinous glands.

GROUP VI, ANTERIOR LOBE PITUITARY HYPERSECRETION

Case No. 12, a boy twelve years of age, is one of hypersecretion of the anterior lobe of the pituitary gland. As has been stated, the anterior lobe pituitary gland has as one of its functions the stimulation of the osseous growth. It has been

termed by some the growth gland of juvenile life. We have known, for instance, children who apparently have stopped growing for a number of years to be stimulated in their growth by the administration of simple preparation of the anterior lobe pituitary gland by mouth and hypodermically. I know of one case of a child who grew five inches in the course of two years. Here is a boy twelve years of age who has an unquestionable overgrowth of the entire osseous system. There is a proportionate overgrowth of all the bones, showing that the condition producing it is more than likely an overfunction of the anterior lobe of the pituitary. You will note that his hand as compared with mine is about one-third larger, and he has a proportionate overgrowth of the short and flat bones, as well as of the long bones. One of his chief complaints is marked irritability and nervous instability. There are mental abnormalities which we have frequently noted with anterior lobe disorder, whether over- or undersecretion.

GROUP VII, RAYNAUD'S DISEASE

WITH DISCUSSION OF RECENT ENDOCRINE TREATMENT

Case No. 13 is a very interesting one of Raynaud's disease. This woman is thirty-three years of age and has had the condition of the fingers which you see, of very marked discoloration and atrophy of the terminal portions of the two middle fingers, symmetrically affected, resulting in amputation of the first phalanx of the middle finger of one hand, due to gangrene. The condition occurred a number of years ago, beginning with vasomotor changes. The fingers then became very blue, then purplish, and finally changed to a white pallor. Following this the terminal phalanx of one finger became gangrenous and had to be amputated. The symmetrical involvement of the fingers, taken with the history of early vasomotor spasm, followed by complete choking off of the blood supply at the ends of the fingers, resulting in gangrene, makes a very positive diagnosis of the rare condition known as Raynaud's disease. Besides this interesting vasomotor spasm of the fingers, she has a very typical adiposity, involving the girdle region, particularly the

inferior, and to a lesser extent the superior girdle. Associated with this she has had a very irregular menstrual life, the periods occurring at intervals of from three to five months and varying in amount and duration of flow. At times she has a metrorrhagia and at other times a very scanty, imperfect flow. This marked irregularity of the periods at the age of thirty-three, taken with the typical girdle adiposity, would make a very classical diagnosis of insufficiency of both lobes of the pituitary gland. She has been examined very carefully by Dr. J. F. Sloan of Peoria, who has noted a number of years ago a decreased metabolic rate and other signs indicating a secondary hypothyroidism, a complication of which we have spoken, in those cases of pituitary disorder which run a prolonged period of time. After the presence of this hypothyroidism for three or four years the function of her thyroid gland changed entirely so as to become oversecreting, and now she has a high basal metabolic rate. In spite of this high basal metabolic rate, however, she has been gaining in weight, which would indicate that she yet has a hypopituitarism with the hyperthyroidism. Dr. Sloan and Dr. Geo. Parker of Peoria have been giving her various ductless gland treatment in order to note any effect upon her Raynaud's disease. She has been obtaining a combination of ovarian and thyroid medication. She states that she is much better under this treatment.

The suggestion that I would make with regard to treatment is to try pituitary treatment in this case. There are now in the literature quite a number of cases of Raynaud's disease, in addition to other vasomotor disturbances, such as scleroderma and even minor dermal changes, as urticaria and erythema, which reacted very well to pituitary treatment. This treatment is given by exhibiting large doses of pituitary substance, posterior lobe, say 10 or 15 grains, in enteric capsules (coated with salol), by mouth, in addition to which is given Pituitrin (0) (Parke, Davis & Company) hypodermically, to the dose producing the intestinal reaction, consisting of abdominal cramps and defecation. The initial dose of Pituitrin (0) is 1 c.c. (15 minims), and this is increased 1 minim each day until intestinal cramps and defecation occur. This is considered the

maximum physiological dose and should not be exceeded for fear of producing the general reaction, consisting of emotionalism, tachycardia, syncope, etc. For a detailed account of pituitary treatment for any of the vasomotor skin diseases or pituitary insufficiency of the anterior or the posterior lobe, we would refer you to an article on "Endocrine Adiposity" in the Clinics of North America, St. Louis Number, Vol. 6, No. 1, 1922.

SECONDARY OPERATIONS FOR GOITRE

EDWARD G. BLAIR, A. B., M. D., F. A. C. S.
KANSAS CITY

The matter of the secondary goitre operation is a very resourceful subject for thought and consideration by those of us who essay to "cure" goitres by surgical procedures. There is nothing more disappointing to the goitre patient than to have passed through an operation with the hope of relief, if not a cure, than to have to be subjected to it a second time, unless that be predicated as a probable necessity.

The conditions which primarily exist in pathological glands, and which may demand a second or even third operation, are practically three in number. The most offending of these three is found in the adenomatous type, where the gland is involved throughout by glandular proliferation, and from which a varying portion of the gland has been removed; and in which the process continues in the residue of gland left undisturbed. This form of *return of the goitre* is chiefly disappointing because of the resultant cosmetic defect after having undergone an operation. The second condition is found in the colloid goitre where a portion of the gland has been removed with anticipation of a recession in the part remaining, but where it persists in a deforming irregularity, with the further possibility of later developing toxicity. The third need of a further operation, after the primary one, may be found in any hyperplastic gland where an insufficient amount of gland tissue has been removed to effect relief of symptoms of toxemia.

We are convinced that all goitres begin as colloid goitres, which increase in size by hypertrophy because there is deposited within the acini an increased amount of colloid material. To accommodate this increase, the cells lining the acini become more columnar and their cellular nucleii perhaps enlarge. From such a goitre, if any symptoms or signs are present, they are due to pressure. We recognize this type as the adolescent goitre without toxic symptoms. This form may persist for a sufficiently long time to permit of a slight increase in the number of

the cells lining the acini; or, in some cases, an increase in the interstitial cells forming the framework of the gland, with or without the production of new acini. Where such acini are believed to have resulted from interstitial proliferation, there may be found within these walls new colloid substance.

All these proliferative forms are hyperplastic, and with any degree of hyperplasia, however small, we find some resultant hyperthyroidism, just as we believe that, without hyperplasia, we find no hyperthyroidism. The former type results in an adenomatous colloid goitre, while the latter is responsible largely for irregular types of former fruste.

Hyperplasia may assume different forms, as it grows from the acinal walls or interstitial tissue. One form of hyperplasia consists of a papillary epithelial proliferation of cells, which is found within the acini, taking up all their space so that there is practically no area remaining in the gland involved for storage or accumulation of colloid material. Such an hyperplasia is always associated with exophthalmic goitre and is supposed to be the only type of gland in which true exophthalmos is found.

Another form of hyperplasia which we will consider consists in proliferation of the acinal cells, either into the lumina of the acini, or between the walls of the acini and into the interstitial framework. Both these forms constitute the adenomatous type of goitre, and this type of hyperplasia usually has associated with it, sooner or later, certain forms of degeneration, and occasionally degeneration with secondary proliferation. *With the degeneration of any goitre there seems to be formed an altered secretion which is extremely toxic to the heart and nervous system, and this is specially true of the old adenomatous colloid goitres.*

In an operative experience of over 1,300 cases we have encountered the need of secondary surgical procedures in twenty-five cases. Two have been in the colloidal types, four in exophthalmic goitres, and nineteen in the adenomatous types. In eleven of the cases the initial operation was done by other operators and mostly in the largest goitre clinics in the United States. Fourteen were our own cases. The reason for making this differentiation is to indicate that in the inception of goitre surgery apparently all operators failed to recognize this possibility. Most of these cases resulted from the early efforts of the operators.

In the effort to reduce the time of operation only the main mass of an adenomatous goitre was attacked, and the remaining portion was not inspected. Then, too, there was ever present fear of removing too much of the thyroid tissue; particularly was this a factor in the colloid and adenomatous types. With the observations made, as time advanced, it became evident that the results were not always satisfactory. Some question arose as to whether the results in these cases justified the risks.

In the last few years it has been demonstrated that the subsequent operation is a safe and satisfactory step, only one fatality having occurred on the fourth post-operative day, supposedly from pulmonary embolism.

In considering the recurrence of the gland after operation, it may be safely said that this feature depends largely upon two factors: First, the amount and location of gland tissue diseased; second, the experience of the operator.

Discussing the first factor, we believe that, with a thoroughly degenerated adenomatous colloid goitre, the probability of recurrence will be present potentially in every case.

We believe that in the exophthalmic having one lobe more seriously affected than the other, a cure may be effected by lobectomy of the badly diseased lobe and resection of a part of the opposite lobe, usually found near the lower pole.

We further believe that a recurrent goitre may be operated on with comparative safety if the perverted secretion has not caused a thyrotoxicosis for too long a period. This may be true, likewise, in further recurrence for a third operation, of which we have had three successful cases.

In the adenomatous type, with more or less complete involvment of the thyroid, it was early evident that lobectomy was unsatisfactory because of the asymmetry resulting from thoroughly clearing one side of the neck, leaving a large mass of irregular thyroid tissue in the other; some effort was made to correct this by placing several deep sutures horizontally into the projecting portion of the gland nearest the median line, tying them tightly, and thus strangling such portions as were inclosed by the sutures. This procedure was of only slight benefit and did not prevent the further growth of adenomatous masses with degeneration, which occurred in the portion left undisturbed. It did, however, encourage the resection of certain isolated gland projec-

tions; and was the inspiration to what later became a complete resection of the remaining lobe.

This resection for recurrence is now definitely and satisfactorily accomplished in two different ways. If the gland is in lobulated formation from above downwards, as is frequently the case, then the most involved or degenerated portion of the gland is selected for complete removal. In the remaining lobules the most prominent one is selected for excision; and about it, in the contiguous thyroid tissue, a chain of deep sutures is thrown and tied, shutting off the blood supply in a measure from the portion to be removed; then the excision is made as the index finger lifts up on the posterior surface of the gland. As the deeper levels are reached the blood supply is not always under control from the preliminary suturing, and one must be prepared to add mattress sutures or others as need arises. When this step has been completed and all active bleeding has been brought under control, through and through sutures are placed in the sectional surfaces and the opening closed, thereby further overcoming any tendency to ooze, or a controlling suture to slip or cut out. In like manner more than one lobule can be removed.

A word of caution is here offered to the novice in thyroid surgery in attempting this performance lest uncomfortable bleeding ensue. Some knowledge must be had of the friability of the tissue; of how much pressure the tissue will bear from the sutures and where they should be placed. Such judgment only experience in goitre surgery will afford.

In the gland formation where no lobulation exists, but the mass is only an irregular structure made up of numerous small adenomatous foci, with little selection of the portion to be sacrificed, the resection should be a horizontal one of either an upper or a lower segment complete, according to which is the better tissue to leave. This section is fortified by a single cross chain of deep sutures and a ligation of the upper or lower pole leading to the segment taken away.

Utilizing again the value of experience, if the operator will make some little search he may discover a portion of normal thyroid tissue with an easy line of cleavage which makes this discard of the adenomatous portion comparatively easy. To be sure a portion of normal thyroid is often found thinned out

and distorted and one must be sure of his structure before making too great a sacrifice of tissue.

In a measure, having established the feasibility of resecting the thyroid gland under all operable conditions, the procedures are much the same as confront the plastic surgeon. Judgment must be directed during the operation to suit the formation and the character of the tissue, and as an essential adjunct to this fact the question necessarily follows: How much of the gland can be removed? It is our experience that this cannot be answered by measurements of portions. This again is a matter of judgment founded upon the history of the case and the character of the tissue as grossly revealed. This much has been established: that more can be safely taken away than has been commonly set down by rule. The more toxic a case is, or the more degenerate a gland is found to be, the greater should be the sacrifice of such tissue. As age advances there is manifestly less need of thyroid tissue; in fact, it is possible for a human being to live with practically no thyroid tissue, *if it be not all removed in one operation,* and an essential amount of glandular therapy furnished to the system afterwards. These facts are specially demonstrated in one outstanding case as reported herewith. Other observations have given us the same impression.

CASE: Miss P. K., dressmaker, age 62, single, white, American. Family history negative. Personal history, negative, except that in adolescence she developed a goiter which, while in evidence, remained quiescent until about the age of 50 years. At the age of 54 years a central mass of considerable size was removed (by another surgeon) and the lateral lobes evidently were not disturbed. After a few months it began to enlarge again slowly on both sides. Eight years later we performed a secondary operation for a large, degenerated bilateral adenomatous development. Without careful inspection of the entire gland prior to lobectomy the right mass was removed, presuming it to be the major portion. On examination of the left portion, however, a much larger growth was detected substernally, which was depressed deeply toward the spine, for which reason it was not at first glance in evidence. On delivery from the neck it was found so totally degenerated, with hemorrhagic areas and calcareous infiltration, that we dared not leave it in; and yet

we hesitated to remove the entire gland. As there was no alternative, practically all of the gland was taken, except small fragments left as substantial stumps for ligation at the poles. These were, of course, strangulated. The paratracheal areas containing what we hoped to be the parathyroid glands were carefully ligated so no injury would result to the parathyroids.

This patient was immediately put on a glandular therapy following operation. She left the hospital and about ten days afterwards discontinued medication.

She seemed to do well at home for several days and then became weak and had twitching of her muscles, particularly of the arms and legs. Her weakness grew rapidly and she became cachectic and emaciated and developed concurrently night sweats. In a few weeks she had become so weak and nervous that she could scarcely lift her head. In this condition we found her about three weeks after she had left the hospital.

She was slightly cyanotic, and had a rapid weak pulse, with a slightly subnormal temperature, nauseated and complained of a tightness in her chest which caused labored breathing and gave her a fear of impending death.

She was at once put on her medication and recovered slowly, under treatment, in about three months. Since then she has been perfectly well so long as she takes her thyroid and parathyroid capsules, but feels the return of the old symptoms when she leaves off.

She did not do well on thyroxin and had to be put back on thyroid medication.

Today, about one and a half years since her operation, she is better, she says, than she had been for twenty years prior to operation.

From the foregoing we wish to conclude with the following observations:

CONCLUSIONS

1. That hyperthyroidism is the result of the secretion from hyperplastic goiters. That the amount of hyperplasia determines the amount of hyperthyroidism.

2. That the type of poison which causes the marked cardiac muscular degeneration and central nervous system deterioration, if not the entire organism, is dependent upon altered thyroid

secretions. That these altered secretions may be due to the degeneration of hyperplastic goiters with formation of leukomains, or again by some action on the other endocrines, the chief of which are the adrenals, causing lost or changed functions to them.

3. That the secondary operations may be definitely deferred by not waiting for involvement of the entire gland, thereby recommending earlier but less radical operation.

4. That the rule of thumb cannot be used successfully in thyroid surgery as to how much gland shall be removed. This depends entirely upon the experience of the operator, as does the result of the operation.

5. That more thyroid tissue can be successfully removed at a secondary operation than is now generally supposed.

6. That secondary operations can be successfully performed. That these should be performed when, if not before, signs of thyrotoxicosis appear.

I have two very interesting cases furnished me by the local men that illustrate some phases of the subject.

This first patient, Mrs. J. P., is a woman, 38 years of age. Twelve years ago the left lobe, isthmus and anterior portion of the right lobe were removed at one of the largest goiter clinics in the country. Three years afterwards the right lobe was obviously increasing in size, and has slowly increased for nine years. As you see, it has crowded the trachea far to the left. One projection fills the supra-sternal notch, and there is probably an intra-thoracic projection on the right side. The pressure symptoms are marked, although not severe.

Four years ago she was thought to have tuberculosis in the right lung, but states that she never had much, if any, fever.

Her pulse rate is 120. The basal metabolism rate plus 10. She is remarkably free from tremor and eye symptoms.

One peculiarity of the case is that her systolic blood pressure is 145, while her dyastolic is only 72.

This patient presents a typical picture of the kind of cases that I have been talking about.

This proliferation of the right lobe should have been removed several years ago when it began to cause trouble. She has fortunately gone nine years without becoming toxic. Undoubtedly some damage to the heart has occurred as evidenced

by the increased pulse pressure, and the sooner she gets rid of it, the better.*

The second case is Mr. B. E. W. Six years ago he was suffering with an extremely severe exophthalmic goiter. A double ligation, performed at one of the largest clinics in the country, gave him no benefit. He returned to that clinic ten weeks afterwards and they advised against operation. Then he came to Bloomington and Dr. Sloan very properly removed most of the right lobe and a portion of the left. He recovered satisfactorily and was in comparatively good health for two years, then the remaining portion of the left lobe began to grow and his symptoms returned. He was subjected to X-ray and radium treatment for twelve months. At first he seemed to get some benefit, then gradually became worse. He made all arrangements to have a second operation and three days before he was to enter the hospital he sustained a cerebral hemorrhage. His right side was completely paralyzed for a time. Since that time his paralysis has been getting some better, but he is still markedly toxic.

This case is a spectacular example of the folly of delay. His only chance now is to have the rest of this left lobe removed.† This should be done as soon as his condition will permit. Had this left lobe been removed two years ago when his symptoms returned he would probably not have had this cerebral hemorrhage. In my opinion its removal at this time will improve his condition greatly.

*"Mrs. J. P." was operated on one month afterward and a soft colloid mass as large as a grape fruit was removed from the right thoracic cavity with the right lobe. Her symptoms that indicated tuberculosis have all disappeared since the operation.

†"Mr. B. E. W." was operated on three days afterward and the left lobe removed. The remains of the left lobe had increased to about eight times the size it was at the time of previous operation. Hyperphlasia was present throughout. The improvement in the general condition of the patient following the operation is most decided.

DIAGNOSTIC CLINIC

DR. W. WAYNE BABCOCK

PHILADELPHIA

9:00 A. M. Friday, January 25, 1924

CASE I: Toxic Adenoma in its Early Stage Exacerbated by Iodine.

This patient is a married woman twenty-nine years old who has had no children. The previous history shows a tendency to melancholia that has been marked during the last few years. For ten years the patient has noticed enlargement of the neck, which she believes has been more marked during the past year. For three months she has been taking two to five drops of tincture of iodine twice a day and finds that she feels no better, that her heart beats rapidly upon exertion, and that the neck has increased in size during the treatment. You will observe the symmetrical swelling of lower anterior part of neck made up of a moderately soft thyroid gland containing a palpable nodule in the left lobe near the isthmus about the size of a cherry. This patient weighed 109 pounds at marriage four and a half years ago and her present weight is 134. She has no tremor or headache, but has complained of palpitation and tachycardia the last six weeks. Apparently we have here a case of Plummer's Disease in the making. This is an adenomatous goiter with early toxic symptoms that have been aggravated by the use of iodine. Now is the time to protect the patient's heart from future degenerative changes, to prevent a future intense thyrotoxicosis. In this patient the prophylactic and curative treatment is both easy and safe. It consists in the enucleation of the adenoma. In this type of thyroid enlargement we know of no effective non-operative treatment.

CASE II: Toxic Adenoma advanced with Myocardial Degeneration.

Our first patient presented a toxic adenoma at the age of 29 years; our second patient shows the same condition 25 years later in life. The patient is a married woman, aged 53, who has had ten children and no miscarriages. She has noticed a thyroid enlargement for twelve years and for the past eight years has shown increasing nervousness and enfeeblement. An operation for pelvic laceration was done eight years ago and the patient thinks her heart has not been as good since that time. For six years she has been in the hospital off and on for severe cardiac disturbances. She was very ill last spring with a generalized edema and, as you see, is now very

weak, and shows marked tachycardia, marked cardiac irregularity and a marked tremor. There is a large bilateral thyroid enlargement, with enlargement of the isthmus and with multiple adenomas, producing a very nodular goiter you may easily recognize even at a distance. On palpation, after the method of Pottenger, of the chest we can make out what seems to be the left cardiac border well to the left of the nipple line, while the right border runs nearly two finger breadths to the right of the sternum. Pulsation of the veins of neck, with irregularity, and a thrill is shown. There is a moderate edema of the legs and the patient is hardly able to walk. The patient shows the advanced cardiopathy with decompensation from a toxic adenomatous goiter of twelve years duration. She illustrates what Doctor Jackson said yesterday, that it usually takes fourteen years or more for these adenomas to develop impressive toxic symptoms, while with the exophthalmic goiter they appear within a few months. Unfortunately, this patient did not accept or receive treatment while it was prophylactic and curative, and now the wreck is so complete that little remains to salvage. Advanced and hopelessly damaged as her heart condition is, let her enter a hospital, be digitalized and treated, with hope that it may even yet be possible to give some degree of relief by a thyroidectomy.

Case III: Goiter with Hypothyroidism Secondary to Tuberculosis.

This patient comes to us with a moderate sized symmetrical enlargement of the anterior part of the neck. She is single and 32 years of age. For many years she had a contact association with a tuberculous stepmother. There has been expectoration, cough and weakness for the last six years, and she has been in a sanitarium for pulmonary tuberculosis for the last four years. Much of the time she has been able to work in the sanitarium as a bookkeeper. The patient's weight when she was admitted to the sanitarium was 92. At present it is 132. There is a persistent evening temperature of 99.4 degrees to 99.6 degrees F. There is no tremor, no tachycardia, and the patient shows no excitement or emotional stress on examination. The thyroid enlargement is quite uniform, rather soft and not vascular. The general expression of features is somewhat heavy and the skin rather pale, dry and thickened. This suggests a hypothyroid condition. An X-ray examination shows areas of fibrosis in both upper and lower pulmonary lobes and the apices. If you read the chest as Pottenger has suggested you will note on simple inspection the areas of subcutaneous atrophy that correspond quite accurately with the underlying pulmonary lesion shown on the X-ray plate. It strikes me that this woman is an example of thyroid enlargement and probably partial thyroid exhaustion, the result of constant demands made upon the gland by a chronic tuberculous toxemia. Infection tends to exhaust the thyroxin storage. There is great danger of overestimating the importance of the goiter and of

ascribing symptoms to a condition that is purely secondary to the pulmonary disease. With a patient of this type the metabolic test is of value, and we will expect a low reading. So often a patient who has had evidence of hyperthyroidism passes on into hypothyroidism, but continues to be treated as a case of thyrotoxicosis. My opinion, then, would be that here is a case of predominant tuberculosis of the lungs, with a secondary enlarged but exhausted thyroid gland. How unwise and how futile would an operation upon the thyroid gland be. Rather should we continue to treat the pulmonary condition and also try and give some relief to the depleted thyroid by iodine or thyroid feeding.

CASE IV: Four Years of Worry as to an Intrathoracic Goiter from an Unconfirmed X-ray Shadow.

This patient is an unmarried woman of 47 who entered a sanitarium for tuberculosis three years ago, and remained three months. When she entered the sanitarium she weighed 104 pounds, had morning expectoration, marked gastro-intestinal disturbances with vomiting, and the physical evidence of an early pulmonary tuberculosis. In the three months that she was in the sanitarium she gained eleven pounds. Since that time her weight has increased so that she now weighs 127 pounds, a gain of 23 pounds. She has a slight cough and slight expectoration. Some years ago she was told she was a bleeder because of hemorrhage following an operation on the nose. While in the sanitarium she had an X-ray examination which is said to have shown a marked enlargement of the thyroid gland, presumably an intrathoracic goiter. Inspecting the chest, we observe an intra-clavicular absorption of subcutaneous tissue, more marked on the right side than upon the left. There is no obvious goiter, no enlargement of the veins of the neck or chest, no evidence of tracheal compression or displacement, no evidence of pressure on the recurrent laryngeal, sympathetic or vagus nerves. This is a patient with the gastro-intestinal disturbances of pulmonary disease, who has no special nervous symptoms, no ocular symptoms, and, as you see, no cervical or thoracic symptoms. She has an arrested pulmonary tuberculosis and comes to us apprehensive from the fact that an X-ray examination indicated she had an enlarged thyroid, although she has no other evidence of thyroid disease that we have detected. This case suggests the danger of an unbalanced dependence upon a machine-made diagnosis. Contrary to the prevalent view, seeing is not necessarily believing with either the X-ray or the microscope. Both must constantly be checked and corrected by clinical observation. We should carefully question every diagnosis made in the laboratory that does not accord with the clinical findings. We should be instructed but never dominated by a laboratory report, and we should constantly realize the thousand and one errors in Roentgen interpretation. In a case like this I have opened the chest, at the insistence of a roentgenologist of international fame, and have found

nothing. It is unfortunate that this patient has been permitted to worry for four years by reason of an unconfirmed shadow on an X-ray plate.

Has this woman hemophilia, a disease usually transmitted by the female, who escapes, to the male, who manifests the delayed clotting time? While it is convenient to blame our post-operation hemorrhages upon hemophilia, we rarely can honestly do so. Surely, if this patient were a bleeder, she would have found it out years before the operation on her nose. Let us, however, determine the clotting time and carefully and judiciously review all of the evidence and, if possible, clear the patient's mind of the two worrying and apparently ill-founded obsessions as to intrathoracic goiter and hemophilia.

Case VI: Neurasthenia with Goiter Phobia.

This patient presents numerous rather interesting symptoms referred to many parts of the body. She is 44 years old, married, and has had two children. Eight years ago she had an operation upon a nasal sinus, preceded fifteen years ago by a severe attack of tonsilitis. Since that time every winter, and nearly all winter, she has had trouble with soreness and choking of the throat. The tonsils are very small, and there is little evidence of disease in the pharynx. She has constantly sought treatment, but of late years the physicians have not introduced their instrument down low enough in the throat to satisfy her. She complains that every night she has constant dryness, soreness and choking in the throat. Her mother died of tuberculosis and the patient has an unproductive moderate cough. She speaks of severe pain and distress in the chest and indeed in every part of the body that is referred to.

This is the type of patient that we have always with us, a patient that suffers constantly and at the hands of many physicians, and really enjoys and devotes herself to miserable health. She has been treated for a great variety of conditions, and often with marked temporary relief, especially if some new or unusual type of treatment were used. If I should wish testimonials for some especially bizarre method of treating disease, I should like to have a series of patients of this type. They give a foundation of reported error for every new ism, cult and pathy, from Perkin's tractors to Abrams' oscilloclast. We are prone to think of these patients as being neurotic, as having symptoms that are functional or auto-suggestive, and as not having organic disease. They pass from physician to physician, as this patient has passed, now getting better, and now getting worse, and much of the time not being relieved at all. They are undernourished and poorly developed, and often show visceroptosis. Frequently, as in this patient, there is a history of tuberculous contact. If we carefully examine these patients we find that a large number of them have enlarged thoracic and mesenteric lymph nodes. They react to tuberculin injections, often violently. It has impressed

me that a very large percentage of these so-called neurotic patients are suffering from a chronic mild form of tuberculous toxemic, manifesting itself by symptoms that are referred to various parts of the body. I am reminded of the fact that the late Weir Mitchell, in his successful treatment of neurasthenia, was using the best treatment for tuberculosis at a time when we did not know how to treat tuberculosis as such. Rest and over-feeding, electricity, fresh air, and elimination of excitement are good things for patients with tuberculosis. I cannot but feel that many of these neurasthenic patients must be looked upon as suffering from mild inactive forms of tuberculosis. They must be protected from the profession, as they crave violent forms of treatment. Particularly do they easily acquire the progressive operation habit. A patient reveals the diagnosis when she has had the coccyx removed and the uterus or kidney suspended. It is a serious responsibility for a physician to start this operative habit. A woman who came to me some time ago had had twenty-eight operations and desired more. It is reprehensible to keep these patients continuously stirred up by local treatments of every accessible organ and to over-emphasize unimportant conditions in tonsils, sinuses, eyes, uterus or other organs. I may be wrong in this case, but it strikes me that the thing she most needs is a good old-fashioned family physician who will advise and protect her and keep her out of surgical clinics, and especially out of group clinics. The best results I have seen in this type have followed the use of tuberculin and an anti-tuberculous regime.

GENERAL CONFERENCE BY DR. BABCOCK

The thyroid gland presents many intricate problems that have led to much diversity of opinion. With a pathology and physiology none too clear in the minds of those who have devoted years to the study of thyroid disease, it is evident that the subject must be a confused or perplexing one to those of us in the medical profession who have not specialized in this field. In an attempt to simplify and elucidate the subject, may not this society go on record? May it not serve as a guide to medical opinion in this field? I am curious to learn if our members do not substantially agree as to many matters relating to the thyroid, and shall therefore state a number of propositions for your discussion, acceptance or rejection. While time limitations will prevent us from touching but a few phases of the subject, I hope that at later meetings these "round table" discussions may be continued and elaborated. Because these propositions are put in affirmative form does not, of course, imply that they represent absolute truths.

1. Excluding inflammatory and neoplastic diseases of the thyroid, the various thyroid enlargements are expressions of different stages or variations in a single pathologic process. The thyroid gland may undergo hypertrophy, hyperplasia, a resting or colloid

stage, atrophy or degeneration. A single gland may pass through all these stages. The hyperplastic or hypertrophic gland is the simple struma, the parenchymatous goiter, or, if toxic symptoms are manifest, the exophthalmic goiter. If the hyperplastic tendency stimulates interstitial epithelial cell rests to growth, an adenomatous or nodular goiter results. Cystic, hemorrhagic, calcareous goiters merely express degeneration changes in the course of the single pathologic process. We should discourage classifications that give these conditions the status of disease entities. As this concept of goiter seems to have your general acceptance, let us take a second proposition.

2. Our concept of the thyroid gland is that it consists of three elements: First, a supporting connecting tissue; second, epithelial elements devoted to the secretion of thyroxin; third, colloid, which has a remarkable affinity for iodine and is devoted to iodine storage. Hyperplasia of the epithelial elements results from excessive functional demands and indicates hyperactivity or thyrotoxicosis. Excessive colloid usually indicates a gland at rest or with hypofunction. Normally, two per cent or more of the gland consists of iodine, if the iodine falls below one per cent, hypothyroidism may develop.

3. Hyperplasia of the thyroid or goiter follow increased physiologic demands, deficient iodine, infection, and removal of part of the gland. The greatest factor in endemic goiter is iodine starvation. As a corollary iodine feeding is the most important prophylactic measure against goiter.

4. The tendency for adenomas to develop in the hyperplastic thyroid is a racial one, absent in many animals, but occurring in the human and the rodent thyroid.

5. Adenomas of the thyroid are not amenable to treatment except by local destruction or eradication. By preventing thyroid hyperplasia we may prevent the formation of adenomas.

6. Infection, partial, excision, increased physiological demands, excite but do not produce goiter, if there is sufficient iodine supplied to the gland. If we supply patients with sufficient iodine during the periods of excessive thyroxin loss, such as puberty, pregnancy, lactation, during the menopause and times of great emotional stress and infection, so that the thyroid always has insufficient iodine in storage, we should prevent goiter. If this be true, should we not as a society spread and promulgate the ideas of iodine feeding. As a corollary is it not better to have only 5 per cent of goiters in a community with three per cent of adenomas excited to toxicity by iodine feeding, than to have 60, 80, 93 per cent of thyroid enlargements in the community and have only one or two per cent of toxic adenomas? Looking to the greatest good to the greatest number, we should be willing to accept the occasional danger from iodine feeding. With a toxic adenoma, the condition runs on for years with symptoms so slightly noticeable that severe cardiac damage usually occurs before the

patient seeks relief. Is it not better to excite these potential toxic adenomas at an early stage and so drive the patient to necessary treatment before the heart has been damaged, rather than to let the patient drift on into myocardial degeneration? The exophthalmic goiter gives a less serious involvement of the heart because the symptoms are more acute and develop within a few months. The toxic adenoma usually progresses 4, 6, 8, 10, 16 years before anything is done for the patient. It would be better if these adenomas were lighted into evident toxicity and enucleated early in the progress of the disease.

Let me turn over these propositions for your discussion.

DR. ARNOLD JACKSON: Theoretically what you say has a great deal in it, but I should hesitate to put it into practice for one reason. We know absolutely nothing of the etiology of exophthalmic goiter. What you say in regard to giving iodine during times of stress and during adolescence to prevent goiter I believe is advisable. Ten per cent of the adenomas develop in children, even in babies of two months, so that you would hesitate to advise giving iodine to children. In regard to giving iodine during pregnancy, I think it is a very good thing. At the time of menopause the same might be shown. It should be governed carefully, patients should be seen every two or three weeks and metabolic rate taken.

DR. ARN: I would be anxious to see how it would work out among the school children. We see 95 or 96 per cent of these children with adenomatous goiter. They should have general examination and not have iodine until they have this examination. You have given me an idea in regard to adenomatous goiters in young children. Four or five per cent will have adenomatous goiter. We hesitate to operate upon them at such an early age and so far have been turning them down. The thought comes to me would it not be wise to give these children iodine to see what effect iodine would have upon young thyroid cases. I do not believe it would excite toxic activity as in the adult, because back in the old days every case that presented itself to the family doctor was given a box of iodine ointment, regardless of whether the goiter was adenomatous or not. The adenomas that I have seen have been in people past thirty years of age. I have never seen adenomas in young children excited by iodine.

DR. ARNOLD JACKSON: Twenty-five per cent of the cases under twenty-five years of age are due to lack of iodine. I think iodine should be given to young children with adenoma in the hope of relieving stress on the gland, and carrying them over the age of puberty and then removing it.

DR. TIMANUS: I am glad to hear this discussion. It happens now that I am just starting this work and am anxious to know definitely about this. I am particularly interested to learn about the possibility of giving iodine to the mother. I think the only way to combat it would be pre-natal.

A few years ago I had a woman with a large adenomatous goiter. She told me that all three of her children were born with large thyroids but they later on receded.

DR. ARN: I think it is very important to give iodine to pregnant women and to rub iodine on the neck, as I stressed in my paper of yesterday.

DR. DRYER, AURORA: Is it not true that adenomas are of foetal origin? If this is the case, why don't they give iodine pre-natally?

DR. MOSCHELLE: Isn't it true that for many generations they have been giving blood remedies, especially in the spring, to purify the system? Many contained iodine, many contained arsenic. Especially were these given to the run-down girls of puberty age, blood out of order, aren't making grades in school, taking music lessons, caught in the stress of modern life, this class of girls were given "blood medicine." I am not in favor of giving the so-called "blood medicine," any more than I am in favor of giving iodine tablets promiscuously to children. If iodine in any form is given it should be given under the guidance of a physician who understands that child. If iodine is given to school children, it should be given under the supervision of the school physician, or someone working in conjunction with him. But is it not possible that the old-time doctor was right in his treatment of some of these types of cases?

DR. ARNOLD JACKSON: I want to compliment Dr. Babcock on his wonderful diagnostic clinic.

DR. BABCOCK: We realize that during the latter winter months and the early spring months there is the least iodine in the system, while the most iodine is found in the fall. This corresponds with the periods of greatest growth. School children grow four times as fast in the fall as in the spring. In answer to Dr. Dryer's question, I believe the term foetal adenoma refers to the histologic structure, which is without colloid filled acini, and does not indicate that the growth developed in the foetus. The proper development of the thyroid gland in the foetus seems to hinge largely upon sufficient thyroxin in the mother, and even an aplastic gland in the new-born may develop under iodine feeding.

DR. MOSCHELLE: This reminds us of the proprietary medicine manufactured by Burroughs & Wellcome Company of London. The sheep ate grass on the Scottish hillsides which was laden with spring rains, and they claimed that glands from these sheep were used in making thyroid extract.

DR. BABCOCK: Another phase of this interesting subject relates to the fragmentary evidence indicating a relation of the thyroid to diabetes. After the experimental removal of part of the pancreas and the production of pancreatic diabetes, the removal of the thyroid gland was followed by an improvement in the hyperglycemia and an increase in the number of the Islands of Langerhans in the remain-

ing portion of the pancreas. In a case of crisis following thyroidectomy in the Johns Hopkins clinic, the blood showed hypoglycemia and the intravenous injection of glucose was followed by the recovery of the patient. Should we consider thyroidectomy as a means of treating certain forms of diabetes?

Editorial

DWARFISM, INFANTILISM, MIDGETS AND LILLIPUTIANS

The laity can be confidently expected to evince interest in bizarre types of human beings, and this morbid curiosity is demonstrated by faithful patronage of "side shows" and vaudeville where opportunity presents for gazing upon midgets, dwarfs and Lilliputians. Kings had their jesters and some of the famous ones can be identified as achondroplastic dwarfs. The medical profession has displayed a similar concern for these tiny people, consequent to which a voluminous literature has accumulated. Considerable confusion has resulted and the discriminating reader is sometimes perplexed by the bewildering multiplicity of terms; types of micromelia are recorded carelessly under the wrong title. Thus true infantilism may be classified as essential dwarfism; or a Paltauf dwarf, a Lorain type, a Brissaud type, or a case of Mongolism may be incorrectly designated as hypophyseal infantilism, thyrogenic or eunuchoidal.

Indeed, it is only fair to admit that no uniform classification has been agreed upon, nor can this be reasonably expected upon the basis of existing knowledge. Moreover, transitional forms occur not infrequently which present difficult differential problems, and make confusion worse confounded. That the incretory glands exercise a profound influence upon the development of some types of dwarfism and infantilism must be clearly recognized, but indiscriminate glandular therapy in all types is not commendable.

Complete maturity demands adult intelligence and psyche, adult stature with normal skeletal proportions, adult genitalia with normal secondary sex characters. Mental retardation in an adult, who has reached normal height and normal sex characters, should not be regarded as infantilism. A primordial dwarf with adult mind and genitalia is not an example of true infantilism. Nor should the term infantilism be applied to a eunuchoid of

normal height, possessing an adult mind. Childhood myxedema (a much better term, by the way, than sporadic cretinism) should not be confused with Mongolism, and neither are instances of true infantilism, even though skeletal undergrowth be a striking symptom in both. Frölich's hypophyseal dystrophy, even though it include skeletal undergrowth, and infantile genitalia is nevertheless to be sharply separated from true infantilism.

True infantilism is perhaps best defined as persistent juvenility, in which the skeleton and its proportions, the genitalia, and the psyche remain childish, the type first described by Lorain. Falta insists that this complex is not a primary ductless gland disease, but that the incretory organs are "childish" secondarily, merely in the same proportion as the remainder of the body. Others would consider this syndrome due to a pure anterior lobe pituitary deficiency. The controversy may be settled before long. "The proof of the pudding is in the eating," and the proof in this instance may be a therapeutic one. Diabetes responded promptly to insulin; and so will infantilism respond to a potent extract of the anterior hypophysis, if lack of this hormone be its cause. But the proof to be conclusive will necessitate not only increase in height, but also development of genitalia and the attainment of adult psyche. Meanwhile, until such a product is available, more extensive use of roentgenology in the differential diagnosis of dwarfism and infantilism is advisable, as recommended by Englebach and McMahon in their recent article on osseous development in endocrine disorders. The appearance of bone nuclei, and the closure of the epiphyseal lines can thus be determined, and this information in correlation with the rest of the clinical picture is important and helpful in recognizing the different types alluded to above.—H. L.

Book Reviews

TRAITE D'ENDOCRINOLOGIE. (Les sécrétions internes au point de vue morphologique, chimique, physiologique, pathologique et thérapeutique.) Prof. C. I. Parhon et M. Goldstein. Tome 1. LA GLANDE THYROIDE. Paper, pp. 467, Jassy, "Viata Romineasca," S. A., 1923.

This volume, the result of painstaking compilation, deals with the anatomy, physiology and physiological chemistry of the thyroid in its normal and abnormal relations. Though the phenomena incident to thyroid hypofunction are discussed satisfactorily and at considerable length, those associated with toxic goiter, especially the hyperplastic thyroid of Graves' disease, are not dealt with sufficiently to be of substantial value to the clinician. Here and there throughout the book casual reference is made to previous observations by the authors themselves, but the work contains little that is new, being essentially an annotated catalog of the observations of others. To those desiring an acquaintance with the literature on the thyroid, this book will serve as a useful guide.—I. B.

EINFUHRUNG IN DIE KLINIK DER INNEREN SEKRETION. G. Peritz, Berl., 1923. S. Karger, pp. 257.

For many medical men books like Biedl's or Swale Vincent's are too long, and small "compendiums" like Weill's booklet too short. To them Peritz' book may be warmly recommended. It gives a critical review of facts that are really known in endocrinology. Pseudoendocrinology has been omitted and the reviewer, therefore, considers this book the best for the use of medical students. Most of the 31 illustrations are very instructive.—J. K.

L'OPOTHERAPIE EN CLINIQUE. A. Sartory, Scheffler & Moinson, Strasb., 1923. Imprimerie Gutenberg, pp. 206.

A book on organotherapy necessarily contains a great deal of nonsense, otherwise it would not treat the literature completely. This little book is one of the good sort. It contains a tremendous amount of nonsense as to the use of eye, skin, heart, etc., but the authors tell only what they have found in the litera-

ture and clearly show that they do not believe much of it. A most important feature of the book is its description of the way in which incretory preparations are manufactured and of how carefully such preparations need to be examined.—J. K.

LES GLANDES ENDOCRINES, LEUR VALEUR FONCTIONELLE. J. Parisot & G. Richard, Par., 1923, G. Doin, pp. 248.

An excellent book containing nearly all of the functional tests recommended for the incretory organs. It is quite original and should be read by all clinicians. How often the bedside clinician would like to know whether the function of an endocrine gland is disturbed! This book nearly always answers such questions as satisfactorily as possible at the present time; the literature is reviewed in an almost complete and in a very critical way. The reviewer considers it, along with Biedl's and Vincent's monographs, as the best work available on endocrinology.—J. K.

INNERE SEKRETION UND ZAHNHEILKUNDE. H. Bacherer, 1923. Berlinische Verlagsunstalt, pp. 92.

The influence of the endocrine organs on the teeth is a rather poorly investigated branch of endocrinology. In this little book an attempt is made to bring together the literature on the subject. Although the author sometimes cites as facts things about which in reality our knowledge is defective (for instance, the pathogenesis of rickets; that the hypophysis is the seat of Fröhlich's disease), the book contains so many interesting and important features that no medical man will be sorry to have read it.—J. K.

Abstract Department

Behavior of Loewe's heart-strip preparations under different conditions. III. Adrenin action. [Das Verhalten des Herzstreifenpräparates (nach Loewe) unter verschiedenen Bedingungen. III. Weitere Versuche zur Kenntnis der Adrenalinwirkung.] Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1923, **199**, 437-456.

Serum and plasma in amounts themselves completely inactive increase the action of adrenin on heart-strips by reduction of threshold and longer duration of action. This is not due to their colloid action, since very small amounts of amino-acids have the same action. The results suggest close dependence of the internal secretions on the diet. Serum and plasma hinder the oxidation of adrenin in Ringer's solution. Their ultra-filtrates have the same action in lesser degree. Amino-acids also possess this property, but carbohydrates only in concentrations which are not reached in the animal organism. Carbohydrates show this action in decreasing degree in the order maltose, lactose, galactose, sucrose, fructose, glucose. The thermostability of adrenin in Ringer's solution is increased by addition of amino-acids. The active group of adrenin is very resistant to hydrogen peroxide, temperature increase, and alkalies, changes in degree of action only appearing after some hours, and in stronger solution either not appearing or being delayed much longer. Hence the rapid disappearance of the rise in blood pressure after intravenous adrenin injection cannot be attributed to oxidative destruction of the adrenin.—A. T. C.

Carcinoma of the suprarenal associated with unusual endocrine manifestations. Keyser (L. D.) & Walters (W.), J. Am. M. Ass. (Chicago), 1924, **82**, 87-88.

The case reported is of interest because enlargement of the thyroid, nervousness, tremor, tachycardia, hyperhydrosis, heat intolerance, dyspnea, choking sensations, precordial distress, increased appetite, increased metabolic rate, and hypertension were associated with suprarenal carcinoma. The dyscrasia of the skin and pilosebaceous systems manifested by erythema, acne, comedones and hypertrichosis, redness of the mucosa, and atrophy of the lingual papillae, weakness, fatigue, alopecia and suppression of menses, the change in voice, the increase in weight, all are suggestive of perverted function of the suprarenal cortex as determined from previous clinical evidence. The hyperglycemia and glycosuria

are difficult to account for. In a cursory review of the literature the authors did not find such an association of symptoms mentioned. The death following operation was of a type suggesting insufficiency of the suprarenal medulla, and the small suprarenal found on the right side more or less confirmed such a view.—Courtesy, J. A. M. A.

Intracardiac injection of adrenalin. Petit-Dutaillis (D.), J. de Chir. (Par.), 1923, **22,** 503-630.

Petit-Dutaillis is prosecutor at Paris, and he is enthusiastic as to the value of local injection of 1 or 2 cc. of the 1:1,000 solution of epinephrin to revive the heart during collapse at operations. In 25 such cases published, permanent resuscitation was realized in 56%. The list of successful cases includes 3 of white syncope under chloroform; the interval in the successful cases was not more than 4 or 6 minutes. The nerve centers will not tolerate an anemia of more than 10 minutes at most. Especially instructive is Henschen's case in which a stab wound of the heart was being sutured and the heart action was stopping; the intracardiac injection revived the heart at once, and the operation was successfully concluded. He advocates introducing the long, fine needle in the fourth interspace, close to the margin of the fifth costal cartilage and close to the sternum, pointing the needle slightly toward the meridian line after the first 2-3 cm., thus injecting the fluid directly into the right ventricle. Necropsies and experiments on animals have demonstrated that the injury of the heart from the puncture is so slight as to be negligible. Artificial respiration and simple massage of the precordial region may be indispensable adjuvants. Some have given **pituitary** extract or strophanthin with the epinephrin, to prolong the action.—J. Am. M. Ass., **82,** 502.

Necessity for caution in the employment of high voltage roentgen rays as therapeutic agent against malignant disease: acute adrenal insufficiency and death sequelae. Smithies (F.), Surg. Gynec. & Obst. (Chicago), 1923, **36,** 61-63.

A case is reported of a man 58 years of age in whom death from Addison's syndrome occurred within 4 months after "deep" roentgen therapy of long duration and very high voltage. The roentgen treatment was for supposed malignancy of the spine which was subsequently shown to have been a faulty diagnosis.—G. E. B.

Cholesterin formation in the animal body (Uber die Cholesterinbildung im Tierkörper). Beumer (H.) & Lehman (F.), Ztschr. f. d. ges. exper. Med. (Berl.), 1923, **37,** 274.

The authors discuss the two views concerning the origin of cholesterol in the organism: (1) (Chauffard's) that cholesterol is synthetized in the **suprarenal** cortex, and (2) (Aschoff's school) that the suprarenal merely acts as a storehouse for the cholesterol

from the food. Some of the important literature supporting and controverting these hypotheses is quoted. The possible relation of the spleen to the origin and deposition of cholesterol is mentioned. Beumer and Lehman took two litters of newborn pups weaned 4-7 days after birth. One of one litter and two of the other were killed for controls and their cholesterol contents determined. The remaining two pups (one of each litter) were fed on almost cholesterol-free diet of separated milk, maize, and cane sugar. They thrived fairly well on this diet. After 4 weeks the pups were killed and their cholesterol contents determined. The cholesterol balance was also determined by examination of the feces, the food intake having been accurately measured. Windaus-Fex method of estimating cholesterol was used. One of the pups showed an increase of 1.069 gms. and the other an increase of 1.561 gms. above their respective controls or twenty times the amount of cholesterol administered in the food. From this the authors conclude that the additional cholesterol was elaborated from substances in the food which are not extractable with ether.—S. Shapiro.

Minor endocrine disturbances. Their metabolic and psychical effects. Brown (W. L.), Brit. M. J. (Lond.), 1923, **ii**, 1073-1077.

Brown points out that it would be difficult to mention a drug which is clearly and beyond doubt of value in the treatment of disease and yet which posseses no known pharmacodynamic effects. Yet many of the extracts in common use have not been shown to have any such action. Even some of those which do cannot be used satisfactorily in substitution therapy. The early triumphs of **thyroid** medication tended to blind one to the difficulties surrounding the use of other glandular extracts in therapeutics. Yet the thyroid is exceptional in containing a definite reservoir of secretion and, by virtue of its duct originally opening into the alimentary canal, retaining the power of having its secretion absorbed by that route. It is perhaps fortunate that many of the preparations in use are inert, or otherwise damage might be done. Thus the injection of **secretin** by liberating an active **pancreatic** secretion may produce digestion of the intestine. It is just as well, therefore, that organotherapy lags behind endocrinology.—J. Am. M. Ass., **82**, 245.

The role of endocrinology in epilepsy. Kern (M.), Am. J. Clin. M. (Chicago), 1923, **30**, 637-641.

Five cases of epilepsy were treated with a mixture of **thyroid, pituitary** and **gonad** extracts. In 4 the treatment was regarded as successful, in the other as a failure.—R. G. H.

Osteomalacia in China. Maxwell (J. P.), China M. J. (Shanghai), 1923, **37**, 625-642.

The disease is common in certain parts of China, but is not attributed to an endocrine origin.—L. G. K.

Familial muscular dystrophy—studies of six cases in one family. Mills (H. P.), Haines (T. H.) & Sessions (M. A.), Arch. Neurol. & Psychiat. (Chicago), 1924, **11**, 43-53.

Detailed metabolism studies were not possible in these cases, but the authors state that the findings obtained would not support the contentions of Janney and his collaborators in reference to the presence of hypoglycemia, as the fasting blood sugar in these cases was within recognized normal limits. The basal metabolism of these 6 subjects does not point clearly to either hyperfunction or hypofunction of the thyroid gland as the etiological factor of progressive muscular dystrophy. The findings in the 6 cases studied vary from minus 22% to plus 10%.—C. E. N.

Racial and familial cyclic inheritance and other evidence from the mouse concerning the cause of oestrous phenomena. Allen (E.), Am. J. Anat. (Phila.), 1923, **32**, 293-304.

Two variations in the usual cycle are described. Evidence is presented of racial differences and familial similarities in cycle length. Therefore, a genetic factor may be operating to partially determine cycle length. Reasons are given for believing that the presence of maturing ova in large follicles and their absence after ovulation or atresia is sufficient to explain the mechanism of oestrous phenomena. The author has isolated an active hormone from ovarian follicles which causes typical oestrous conditions in previously spayed animals, thus demonstrating the above conclusions. The continuation of ovogenesis during sexual maturity affords a distinct age difference in successive generations of ova and suggests a logical reason for their maturation at definite intervals.

—Condensed from Author's Abst.—W. J. A.

Experimental transformation of sex in the domestic fowl by precocious ovariotomy (Transformation expérimentale du sexe per ovariotomie précoce chez le poule domestique). Benoit (J.), Compt. rend. Acad. d. sc. (Par.) 1923, **177**, 1074-1077.

Two leghorn pullets, ovariotomized at 26 and (left side) at 4 days respectively, developed male characteristics in a few months. Exploratory laparotomy revealed an organ resembling a testis, and showing (in the first case) typical seminiferous tubules and even spermatozoids. After removal the secondary male characteristics disappeared.—A. T. C.

Cyclic variation in uterine and tubal contraction waves. Corner (G. W.), Am. J. Anat. (Phila.), 1923, **32**, 345-351.

There is, as part of the mechanisms of the oestrous cycle, a variation in the rhythm of spontaneous contraction of the uterine and tubal musculature. Small, rapid, undulatory contractions appear

in the tube of the pig just before the discharge of the graafian follicles, persist during the 3 days' time in which the ova are en route through the tubes, and disappear about the time the ova enter the uterus. The time of appearance of the undulatory contractions in the uterine musculature is synchronous with the period in which the ova, lying free in the uterus, either degenerate (if unfertilized) or begin the blastocyst stage of embryonic development. Upon the basis of these facts Corner has developed the hypothesis that the uterine and tubal contraction cycle represents a mechanism, probably peristaltic in nature, by which the ova are transported through the tubes and uterus.—Condensed from Author's Abst.—W. J. A.

Sex development and behavior in female patients with dementia praecox. Gibbs (C. E.), Arch. Neurol. & Psychiat. (Chicago), 1924, **11**, 179-194.

A definite masculine type of pubic hair distribution occurred four times more frequently in the 310 psychotic patients than in the 235 nonpsychotic pregnant controls. Masculine type of pubic hair occurred in one out of every five patients with dementia praecox between the ages of 20 and 29, which was over five times more frequent than in normal controls and three times more frequent than in patients of other ages.—C. E. N.

The oestrous cycle in the opossum. Hartman (C. G.), Am. J. Anat. (Phila.), 1923, **32**, 353-421.

The opossum is polyoestrous, having a single continuous breeding season from January to October, inclusive. Ovulation is spontaneous and occurs, on the average, every 28 days. Cyclic changes in oviduct, uteri, lateral vaginal canals (marsupial structures), vagina, and mammary glands are described and correlated with cyclic events in the follicular apparatus of the ovaries. In the living animal cyclic changes in the vaginal content were also followed; likewise the wave of growth and subsidence of the mammary glands. Fundamentally, these changes are similar to those in the Eutheria thus far studied and are due to the same stimuli; but the differences have proved instructive. Striking pseudopregnant phenomena of uteri and mammary glands are confirmed. Simple glands are found in the ampullae of the oviducts. They are probably responsible for the secretion of the shell membrane of the marsupial egg, hence homologous to similar glands of the Sauropsida.

—Condensed from Author's Abst., W. J. A.

Ovarian insufficiency. Hutton (J. H.), Illinois M. J. (Oak Park), 1924, **45**, 37-41.

This is a good general review of the physiology of the ovaries in their normal and abnormal relations, the interrelationship of the ovaries with the other ductless glands, and the symptomatology and

treatment of ovarian insufficiency. Ovarian residue administered by mouth, subcutaneously or intravenously, is considered the best treatment.—I. B.

The mechanism of the sexual cycle, with special reference to the corpus luteum. Loeb (L.), Am. J. Anat. (Phila.), 1923, **32**, 305-343.

Loeb holds that the sexual cycle has periods which are successively under the control of the developing ovarian follicle and the corpus luteum. An analysis of the mechanism of the sexual cycle as a whole and a new classification of its periods are given; it is shown that the recent observations of Long and Evans in the rat and of Allen in the mouse are in agreement with the author's main conclusions, and that we must assume that in the rat and mouse the corpus luteum phase of the sexual cycle is rudimentary.

—Condensed from Author's Abst., W. J. A.

Factors which cause cancer and the rapidity and frequency of cancer transformation (Rapports quantitatifs entre les facteurs qui causent le cancer et la rapidité et la fréquence de la transformation cancéreuse). Loeb (L.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 307-308.

In the study of spontaneous mammary cancer in the mouse 2 factors emerge—heredity and ovarian internal secretion. Removal of the ovaries is an absolute preventive if carried out at a sufficiently early age. Once ovarian function is established, removal of the ovaries diminishes the frequency of occurrence in proportion to its early performance, but this procedure has no effect once the neoplasm has started.—Physiol. Abst., **8**, 423.

The behavior of the germinal epithelium in testis grafts and in experimental cryptorchid testes (rat and guinea pig). Moore (C. R.), Science (N. Y.), 1924, **59**, 41-44.

Testis and ovarian grafts made subcutaneously, intramuscularly, and intraperitoneally into normal females and normal males on recovery showed active cell division in the tubules. No spermatozoa were found. If the testicle is held in the peritoneal cavity the germinal epithelium degenerates and the interstitial tissue is increased. Grafts of testis made into the scrotum later showed some normal tubules possessing spermatozoa. The increased temperature is held to be an important factor in producing degeneration in the germinal epithelium when grafts are made elsewhere than the scrotum.—G. E. B.

Oestrous in mammals from a comparative point of view. Papanicolaou (G. N.), Am. J. Anat. (Phila.), 1923, **32**, 285-292.

The author calls attention to the varieties of oestrous in dif-

ferent mammals and to the fragmentary and incomplete condition of our present knowledge of the oestrous problem.

—Condensed from Author's Abst., W. J. A.

The influence of the uterus and the ovary on development of the mammary gland (Uber den Einfluss des Uterus und der Ovarien auf die Entwicklung der Brustdrüse). Plaut (R.), Ztschr. f. Biol. (München), 1923, **79**, 263-276.

Injections of lipoid extracts of **placenta** produce with young animals (guinea pigs, rabbits, cats) of both sexes, at first growth and secretion of colostrum, afterwards arrest of development, and finally degeneration; no formation of gland tissue. The extract has no effect upon adult males. The lipoid extract of the ovary produces a growth of the uterus and appendages in young animals, and is without effect upon the mammary gland only if the uterus is present.—Physiol. Abst., **8**, 532.

X-ray stimulation of the ovary (Reizbestrahlung der Ovarien). Schönhof (C.), Wien. klin. Wchnschr., 1923, **36**, 877.

A girl of 22 began to gain weight; menstruation gradually ceased; abnormal hair growth appeared and there was hypoplasia of the generative organs. X-ray treatment caused loss of the abnormal hair and return of normal menstruation. Similar results were secured in a second case of amenorrhea.—J. K.

The general morphological and physiological significance of the oestrous problem. Stockard (C. R.), Am. J. Anat. (Phila.), 1923, **32**, 277-283.

The usefulness of the vaginal smear method in determining the exact stage of the oestrous cycle is pointed out. The problem thus becomes, in the author's striking phraseology, "not an ordinary histological or morphological one, but a problem in living morphology." The cycle of morphological changes, which may be very readily recognized, gives an indicator for the occurrence of most complex physiological reactions which thus lend themselves to the morphological method of analysis.

—Condensed from Author's Abst., W. J. A.

The adult equivalent of the Froelich syndrome. Abbott (G. P.), Calif. State J. M. (San Fran.), 1924, **22**, 20-21.

There is a type of **hypopituitarism** in adults, of subacute onset, which in many respects resembles the juvenile Froelich syndrome. Its etiology is traceable to infections, especially influenza and measles. The condition is characterized by adiposity, scanty menstruation or amenorrhea, lassitude and headache. Though the adiposity and amenorrhea are not influenced by pituitary or ovarian

opotherapy, the headache and lassitude are relieved by feeding whole pituitary.—I. B.

Further investigation on the oxytocic-pressor-diuretic principle of the infundibular portion of the pituitary gland. Abel (J. J.), Rouiller (C. A.) & Geiling (E. M. K.), J. Pharmacol. & Exper. Therap. (Balt.), 1923, **22**, 289-316.

The oxytocic substance of the infundibulum was isolated in such a degree of purity as to be from 1000 to 1250 times more active for the virgin guinea pig's uterus than the equivalent amount of the acid phosphate of histamine. The product, a tartrate, caused pronounced contractions of the virgin guinea pig's uterus in a dilution of 1:18,750,000,000. This product possesses pressure, diuretic, and respiratory properties. All these properties are believed referable to one and the same substances.—G. E. B.

A preliminary therapeutic study of the active principle of the infundibular portion of the pituitary gland in four cases of diabetes insipidus. Abel (J. J.) & Geiling (E. M. K.), J. Pharmacol. & Exper. Therap. (Balt.), 1923, **22**, 317-328.

The substance referred to in another paper as the oxytocic-pressor-diuretic principle of the infundibulum when used therapeutically showed distinct antidiuretic properties.—G. E. B.

The mechanism of diabetes insipidus (Sur le mécanisme du diabète insipide). Camus (J.), Gournay (J. J.) & Fiterre, Compt. rend. Acad. d. Sc. (Par.), 1923, **177**, 289-291.

Polyuria following lesions in the opto-peduncular region in the base of the brain is accompanied by marked lowering or total disappearance of uric acid from the urine. If the onset of polyuria is delayed the uric acid may disappear earlier. Purine bases and phosphates are increased. These phenomena occur in dogs with experimental polyuria lasting only some days, and also with permanent polyuria (over 4 years). Since caffeine and theobromine are diuretics, it is suggested that the diuresis is connected with degradation of nucleoproteins and excess formation or non-transformation of diuretic purine bases.—A. T. C.

Pituitrin in the treatment of asphyxia pallida neonatorum. Cormack (J. G.), China M. J. (Shanghai), 1924, **38**, 42-43.

Two refractory cases of extreme asphyxia of new-born Chinese infants are reported in which prompt initiation of breathing followed intramuscular injections of 0.3 cc. of pituitrin.—R. G. H.

Degeneratio adiposogenitalis. Hirsch (O.), Wien. klin. Wchnschr., 1923, **36**, 822-823.

In a man of 36 with tumor of the hypophysis and symptoms of

Fröhlich's disease x-ray therapy had no influence. The patient became almost blind. Operation was performed and 4 months later in both eyes visual acuity was 6/8 and the visual fields were nearly normal. The tumor was an adenoma. A woman of 46 was observed with cyst of the hypophysis. One eye was blind; the other showed 1/20 acuity. After operation the second eye became normal. Twice recurrence of the tumor made an operation necessary.—J. K.

Acromegalic gigantism with dystrophia adiposogenitalis (Gigantisme acromegalique avec syndrome adiposo-genital). Schaeffer (H.) & Denoyelle, Rev. neurol. (Par.), 1923, **30**, 346-350.

Report of a case of infantile gigantism, subsequently acromegaly, with the syndrome of dystrophia adiposogenitalis fruste. This case is discussed in reference to the work of Camus and Roussy and Bailey and Bremmer in discriminating between the manifestations of a disturbance of the hypophyseal function and that of a center in the infundibulum. The occasional association of acromegaly and dystrophia adiposogenitalis does not seriously militate against the nervous origin of the latter, as it is possible that this condition is the result of compression of the neuro-vegetative center by the progressive development of a hypophyseal neoplasm.—C. E. N.

The production of the adiposogenital syndrome in the rat, with preliminary notes upon the effects of a replacement therapy. Smith (P. E.), Walker (A. T.) & Graeser (J. B.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 204-206.

The authors have a method of injuring the **hypophysis** without damaging the brain. After this operation one rat showed a cessation of the oestrous cycle and reduction in size of the **ovaries** and uterus. Injections of anterior lobe substance restored ovulation. This experiment is cited as strong evidence of the hypophyseal etiology of the Fröhlich syndrome.—J. C. D.

The seat of action of insulin (Uber den Angriffspunkt des Insulins). Ahlgren (G.), Skandin. Arch. f. Physiol. (Berl. & Leipz.), 1923, **44**, 167-185.

Fresh tissue substance from normal and from totally depancreatized animals was used. Capacity for decolorizing methylene blue was utilized as a measure of respiration. Tissue which did not utilize glucose spontaneously did so after the addition of suitable amounts of insulin. Fructose and galactose were utilized without insulin. Insulin did not hasten the oxidation of beta-oxybutyric acid and lactic acid.—G. E. B.

Normal standards in treatment of 100 cases of diabetes with insulin. Barach (J. H.), J. Am. M. Ass. (Chicago), 1924, **82**, 347-351.

Barach emphasizes the fact that in determining the diet of the diabetic patient three primary needs must be met: (1) caloric requirement; (2) maintenance of protein requirements of the body; (3) if the carbohydrate, protein and fat are given in wrong proportions, certain diseased states of the metabolism—ketosis—will follow with deadly effects. Present-day authorities on metabolism are generally agreed that 1 gm. of protein per kilogram of body weight is a safe protein ration. The largest amount of carbohydrate is given that the patient can tolerate without glycosuria and hyperglycemia. Sufficient fat must be given to meet the caloric requirement of the patient, avoiding large amounts which predispose to ketosis. The total glucose in these diets is estimated by adding the carbohydrate plus 58% of the protein plus 10% of the fat. Ladd and Palmer have adopted the simple ratio of 4 gm. of fat for each gram of carbohydrate in the diet. That 58% of the protein is directly available as carbohydrate has not yet been proved to the satisfaction of all workers in metabolism. Every-day experience with diabetic patients has shown Barach that the nervous make-up of diabetic patients of the same age, height and weight is an important factor in determining the food requirements for active life. The various formulas now in use do not and cannot include this variable factor, and therefore are not so applicable as they may seem. Barach believes, with Allen, that the arbitrary rule of estimating the metabolic needs of the diabetic patient by theoretical calculations is inaccurate, but he does not lend himself, as Allen does, to guess at the diet. In the absence of a better method and one which is beyond criticism, Barach follows the normal diet as near as the patient's diabetic state will permit. So-called normal diets, based on municipal statistics, are on the basis of carbohydrate, 67%; protein, 16%, and fats, 17% of the total. For the needs of the hospitalized ambulatory patient 30 calories per kilogram of body weight is allowed. The diabetic patient cannot assimilate the normal amount of carbohydrate. Experience in 100 hospital cases this year has shown that only one patient could take more than half the normal amount of carbohydrate. The diabetic patient does not do well on excessive protein. A normal diet offers about 1.25 gm. of protein per kilogram. Allowing a nearly normal amount of protein, 1 gm. per kilogram and as much carbohydrate as the patient can take, the remaining caloric requirement is furnished in fat. Being guided by the glucose output in the 24-hour specimen of urine, averaging this output every 2 or 3 days, the carbohydrate intake is reduced from time to time as needed. At each reduction of carbohydrate, fat of equal caloric value is added. Ordinarily the patient is made sugar free in 6 to 10 days. If by this process of exchange the patient cannot be rendered sugar free or attain nearly a normal blood sugar on a satisfactory maintenance diet without the presence of acetone or diacetic acid in the

urine, insulin is added in the treatment, enough being given to allow the patient a carbohydrate and fat intake for a good maintenance. At the time of leaving the hospital, the patient is usually taking 35 calories per kilogram, having gradually worked up to this point. A detailed survey of the first 35 patients showed that at the end of the year 13 were taking more food, and in 20 it was thought best to continue the same diet. In one case it was found necessary to lower the total food intake. In these 35 patients 27 are taking the same dosage of insulin. Seven are taking less insulin than they did when leaving the hospital, and in 5 it was necessary to increase the amount of insulin to maintain the total food tolerance and the desired nutritional state. In the 5 taking more insulin, intercurrent acute infections seemed to precede, if they were not the main cause, of the lowered tolerance. In these 35 cases there was a weight increase in 25 ranging from 3 to 30 pounds (1.4 to 13.6 kg.). In 8 there was no increase, and in 2 there was a loss of weight. Six patients gained 2 to 6 pounds (1 to 2.7 kg.). Nine patients gained from 5 to 10 pounds (2.3 to 4.5 kg.). Five patients gained from 10 to 20 pounds (4.5 to 9 kg.). Five patients gained from 20 to 30 pounds (9 to 13.6 kg.). Of these 35 patients, the outlook is good in 26. These are practically without conditions. In 9 cases the outlook is fair. Of those in whom the outlook today is only fair, it is evident that better conditions in the home and economic betterment would tend to place them in the more favorable class.—Courtesy A. M. A.

The effect of the oral administration of alcohol upon the blood sugar of rabbits. Blatherwick (N. R.), Maxwell (L. C.) & Long (M. L.), Am. J. Physiol. (Balt.), 1924, **67**, 346-347.

When insulin dissolved in dilute alcohol is given by stomach the blood sugar is decreased as much as 30%. Further investigation led the authors to believe, however, that the alcohol alone is responsible for this decrease and that there is no absorption of insulin.—T. C. B.

Treatment of diabetes with insulin. Blum (L.), Carlier & Schwab, Bull. Soc. méd. d. hôp. (Par.), 1923, **47**, 1789-1797.

The authors relate several clinical histories showing the dangers of suspension of insulin treatment in severe cases of diabetes. In a man of 35 the fatal intoxication began 48 hours after the last injection, and death occurred 5 days later. He had been treated with insulin at the hospital and continued the injections on returning home until his supply failed and he had to stop. Increasing weakness set in and was followed by coma. In their second case, the number of injections was reduced after the patient had asked that they be interrupted. Glycosuria and acetonuria reappeared and increased rapidly. Forty-eight hours later the patient

was in coma. Very large doses of insulin were injected immediately, and 24 hours later the intoxication disappeared. Similar disturbances during treatment are due to complications which lower the carbohydrate tolerance, making thus the doses insufficient. They believe that the danger of discontinuing the injections lies in the lack of preparedness of the organism for the acid intoxication. The danger is less in children than in adults, because the islands may have regenerated in children. Diabetics should always keep a reserve supply of insulin to continue the treatment, and to cope with unforeseen complications susceptible of aggravating the diabetes. If they have to discontinue the injections, they should fast and use large amounts of alkali. Only when the urine is alkaline can immediate danger be considered averted.

—J. Am. M. Ass., **82**, 423.

Some effects of insulin and glucokinin on maize seedlings. Ellis (M. M.) & Eyster (W. H.), Science (N. Y.), 1923, **58**, 541-542.

In solutions of 1.0% to 0.005% growth was retarded in proportion to the amount. In weak solutions (less than 0.005%) some beneficial effects were shown.—G. E. B.

Basal metabolism in diabetes (Ueber der Grundumsatz bei Diabetes mellitus). Feyertag (H.), Wien. klin. Wchnschr., 1923, **36**, 823.

Falta, disagreeing with Benedict, Joslin and others, has always stated that even in the most serious cases of diabetes the basal metabolism is not increased. The author examined 3 serious cases of diabetes and studied the basal metabolism with and without insulin treatment. No difference was seen after injection of insulin. This is an argument in favor of Falta's theory.—J. K.

The insulin treatment of preoperative and postoperative nondiabetic acidosis. Fisher (D.) & Snell (M. W.), J. Am. M. Ass. (Chicago), 1924, **82**, 699-700.

Two cases of preoperative acidosis due to starvation and incessant vomiting induced by an acute abdominal condition are reported. The action of insulin and glucose was specific. A third case of postoperative acidosis of a rather severe degree was practically unchanged at the end of twenty-four hours by the use of glucose alone by rectum. The subsequent administration of insulin brought about an immediate disappearance of the ketosis.

—Courtesy A. M. A.

Attempts to maintain the life of totally pancreatectomized dogs indefinitely by insulin. Fisher (N. F.), Am. J. Physiol. (Balt.), 1924, **67**, 634-643.

Some pancreatectomized dogs can be kept alive for at least 8 months. The normal body weight is not maintained, and there

is polyphagia and polyuria, even when no sugar is present in the urine. Others die in spite of insulin control of hyperglycemia. The determining factor for survival seems to be a regeneration of pancreatic tissue from the duodenal stump of the duct.—T. C. B.

Insulin as an investment for the patient with diabetes mellitus. Fitz (R.) & Murphy (W. P.), J. Am. M. Ass. (Chicago), 1924, **82**, 435-438.

There are two classes of diabetic patients: those to whom insulin is a necessity and those to whom insulin is a luxury. Fortunately, diabetes is inherently a mild disease, tending to occur in people past the middle period of life and often lasting for years without producing any notable disability. Therefore, the group of patients to whom insulin is a necessity is comparatively small and does not represent more than a third of any large series. As a general rule, insulin should be given in all cases of diabetes occurring in children and in people under 40; in all cases of coma or severe acidosis; in all cases complicated by an infectious process which has caused either a temporary or a permanent lowering of tolerance; in all cases of proved severity in which there is necessity for a surgical operation, and in all cases in which the tolerance without insulin, as determined by adequate dietetic control, is so low as to make efficient living impossible. No one should hesitate to urge such patients to take insulin at all costs, for the drug may be life-saving and almost always represents a sound financial investment for the patient, with a big dividend of strength and vitality. Insulin, on the other hand, is a luxury for patients with mild diabetes who are seen most commonly. Almost all of these patients, if the disease is uncomplicated, have a high tolerance and do well for years on a reasonably restricted diet. Insulin offers them but little as a financial investment. If patients of this type wish to take small doses of insulin and can afford it, there may be no reason why they should not, and for a few cents' worth of insulin a day add a certain amount of extra food to their diets. They should not, however, be advised to take the new drug; rather should they be encouraged to get along without it as far as possible, or to use it sparingly. The discovery of insulin marks a wonderful advance in the treatment of diabetes, but it must not be abused. The best economic use of insulin will be made by the conservative practitioner, who saves money for the majority of his diabetic patients by keeping them sugar-free and in good condition without the trouble and expense of the drug, but who holds it in reserve for his severer cases for use in as large amounts as are necessary to produce definite results.—Authors' Conclusions.

Physiological action of insulin (Sur l'action physiologique de l'insuline). Gonzalez (P.) & Carrasco Formiguera (R.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 1237.

In general, from the point of view of the onset of convulsions, the less the weight of the rabbits, the more sensitive they are to insulin.—T. C. B.

Basal metabolism in experimental diabetes (La dépense de fond dans le diabète pancréatique expérimental d'après les échanges gaseux. Action de l'insuline sur cette dépense). Hédon (L.), Compt. rend. Acad. d. sc. (Par.), 1924, **178**, 146-148.

The basal metabolism is increased in dogs after total pancreas removal by from 30 to 40%. This cannot be entirely due to disturbance in carbohydrate metabolism, since dogs in which at complete pancreatectomy a small portion was transplanted under the skin of the abdomen and which showed no glycosuria showed a marked increase in basal metabolism, which was not further increased after removal of the transplant and onset of glycosuria. The total gaseous exchange is markedly increased after total pancreas removal, and injection of insulin sufficient to cause the disappearance of glycosuria and lowering of blood sugar to normal, although it increases the respiratory quotient, does not restore the total gaseous exchange to normal. The increase after total pancreatectomy probably is due to increased protein and fat catabolism, independent, to a certain degree, of the carbohydrate disturbance.—A. T. C.

The presence of an insulin-like substance in gastric and duodenal mucosa and its relation to gastric secretion. Ivy (A. C.) & Fisher (N. F.), Am. J. Physiol. (Balt.), 1924, **67**, 445-450.

An insulin-like sugar reducing substance is present in hog's gastric and duodenal mucosa, but is much less than in cattle's pancreas.—T. C. B.

Treatment of diabetes (Zur Therapie der Diabetes). Jaksch Wartenhorst (E.), Wien. klin. Wchnschr., 1923, **36**, 844.

The author found that administration of some ethereal oils or allyl compounds prevents the unfavorable effects of insulin. Some cases of glycosuria are not benefited even by large quantities of insulin.—J. K.

The routine treatment of diabetes with insulin. Joslin (E. P.), Tr. Ass. Am. Physicians (Phila.), 1923, **38**, 374-381.

If insulin is to serve its purpose, it must be emphasized that successful treatment of diabetes mellitus depends upon the utilization of all approved measures without insulin. Adherence to the proper diet, avoidance of extreme undernutrition or overnutrition, and a method of life compatible with the strength such a diet affords constitute the guiding principles in the treatment of diabetes. Since insulin does not cure diabetes, but is merely a val-

uable aid in treatment, the education of the family physician and the patient in the intelligent use of insulin is of vital importance. The learning of the essential diabetic arithmetic is a matter of but an hour's study. The diet must not overbalance the drug, else glycosuria will result; on the other hand, the drug must not overbalance the diet, as this may lead to a dangerous reaction. Diabetic coma is a diabetic accident, and, like all accidents, to be avoided.—I. B.

Action of insulin on rats deprived of the suprarenals (Action de l'insuline sur les rats privés de surrenalés). Lewis (J. T.), Compt. rend. Soc. de biol. (Par.), 1923, **89**, 1118-1119.

The lethal dose of insulin was 10 mgm. per 100 gm. in healthy control rats, while it was only 1 mgm. per 100 gm. in rats deprived of the suprarenals.—T. C. B.

Xanthoma diabeticorum. Major (R. H.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1059-1064.

The patient is a married white male, a farmer, aged 33, who was admitted to the hospital for the treatment of diabetes of approximately 18 months' duration. He is a member of a family of 12 children, 5 of whom have had diabetes, 3 dying of the disease. Two weeks prior to admission the patient noticed a rather "profuse" skin eruption over the chest, abdomen, and extensor surfaces of the forearms and thighs. This appeared quite suddenly and simultaneously and was not accompanied by itching or other disagreeable sensation. Examination proved the eruption to be xanthoma diabeticorum, a rare complication of diabetes mellitus. The condition is produced by a deposit of cholesterol, fat and lipoid bodies beneath the skin. Successful treatment of the diabetes, including the administration of insulin, resulted in the disappearance of the skin condition.—I. B.

Insulin treatment of the toxemic vomiting of pregnancy. Thalhimer (W.), J. Am. M. Ass. (Chicago), 1924, **82**, 696-699.

Thalhimer has treated three patients with severe, toxemic vomiting of pregnancy with a combination of hypodermic injections of insulin and the intravenous administration of glucose solution. The results have been striking, and parallel exactly the results in all patients with postoperative acidosis similarly treated. Thalhimer cautions that only pure, tested glucose should be used in preparing the glucose solution. A 10% solution is convenient to use, as with it the patient receives a fair amount of much needed water along with the glucose. The solution should be run in slowly, about 200 to 300 cc. an hour, and it is important that it be kept warm; 1,000 cc. is the amount usually given at a time. About fifteen minutes after the injection is started, about 10 units of insulin is given hypoder-

mically (i. e., 10 of the new U-iletin units). At intervals thereafter 10 units is given until for 100 gm. of glucose (1,000 cc. of 10% solution) 30 units of insulin is given. One unit of insulin (U-iletin) causes the utilization of from 2 to 3 gm. of glucose, but for safety a slight excess of glucose should be given to prevent a hypoglycemic reaction of insulin shock. It is wise to have epinephrin available for hypodermic use for treatment of a hypoglycemic reaction. Up to the present, however, this has never been needed. Insulin has been demonstrated to have as rapid a curative effect on ketosis and the toxemic vomiting of pregnancy as it has on preoperative and postoperative nondiabetic acidosis. This evidence suggests that the field of insulin therapy may be extended to other nondiabetic conditions.—Courtesy, A. M. A.

Pancreas hormone and sugar utilization (Pankreashormon und Zuckerverwertung). Wertheimer (R.), Wien. klin. Wchnschr., 1923, **36**, 805.

In normal persons the author found that arterial blood contained much more sugar than venous blood. This proves that the normal tissues use sugar. Whether the tissues burn the sugar or whether they change it into glycogen is not known. In severe diabetes the quantity of sugar in arterial and venous blood is the same. The author then examined dogs before and after extirpation of the pancreas and found that after the operation the difference between arterial and venous blood sugar disappeared. He concludes that the cells require the pancreas hormone to enable them to utilize sugar.—J. K.

A German insulin. Zuelzer (G.), Med. Klin. (Berl.), 1923, **19**, 1551-1554.

Zuelzer reports that he had an active pancreas hormone which he called Acomatol ready at the beginning of the war, but he did not use it because it produced spasms in dogs. He attributed this to a toxic action of the preparation instead of recognizing it as an indication of its potency. The war prevented further research. He also had the same intention as Macleod to prepare the hormone from the isolated islands of fish pancreas, but the medical faculty of the University of Berlin refused to grant him the means for the necessary journey to Naples. His method of preparation is different from that of insulin. The product is titrated against epinephrin.
—J. Am. M. Ass., **82**, 252.

The size of the parathyroids of rats and the effect of a diet deficient in calcium. Luce (Ethel M.), J. Path. & Bacteriol. (Edin.), 1923, **26**, 200-206.

Rats on a calcium-deficient diet showed a consistent enlargement of the parathyroid gland, which was due to hyperplasia and

not to cell hypertrophy and which increased progressively with the length of time of calcium-deficient feeding. There was no relationship to sex.—Chem. Abst., **17**, 2908.

Tetany cured by thyroid and parathyroid transplantation (Nach Epithelkorperchen und Schilddrüsen-transplantation beheilte Tetanie). Maier (P.), Wien, klin. Wchnschr., 1923, **36**, 736.

After a goiter operation in a woman of 33 **myxedema** and tetany developed. She was cured by transplantation of a parathyroid and a piece of thyroid of a horse.—J. K.

Action of parathyroid extract (Einige Beobachtungen über die Wirkung von Parathyroidin). Mandelstamm (M.), Ztschr. f. d. ges. exper. Med. (Berl.), 1923, **35**, 370.

Though much experimental work has been expended on the effects of removal of the parathyroids, very little is known of the results of parathyroid hyperfunction, and the few experiments detailed in this paper are therefore of some interest. Rabbits were injected daily with a watery extract of horse parathyroid in increasing doses. The most interesting effect noted was definite protrusion of the eyeball, resembling the exophthalmos of **Graves' disease**, a result which is rarely produced in animals by **thyroid** administration. Other symptoms were increased appetite, restlessness, and a heightened excitability to the galvanic current. It is suggested that parathyroid injections produce overaction of the thyroid.

—Med. Sc., **9**, 309.

Malignant epithelial thymoma. Report of a case with necropsy. Foot (N. C.) & Harrington (H. H.), Am. J. Dis. Child. (Chicago), 1923, **26**, 164-178.

A colored girl 2 years of age had given symptoms for over a year of difficulty in swallowing, paroxysms of coughing and strangling while attempting to drink, but apparently had no pain and no dyspnea except when coughing. The child died suddenly of cardiac failure after being two months in the hospital. Necropsy showed a tumor which was intimately adherent to the chest wall on the left and had forced the left lung downward and backward, compressing it until it was a mere mass of flabby material. Examination revealed it to be a thymona, which the authors believe to be primary and exhibiting a predominatingly reticular type of growth. They think this is the fifth case of primary epithelial thymoma to be reported and the only one occurring in a child.—M. B. G.

A case of ligneous thyroiditis associated with high-grade dental infection. Bohan (P. T.), Med. Clin. N. Am. (Phila.), 1924, **7**, 1069-1074.

The patient was a married woman, aged 38, the mother of 4

living children. The family history was negative. Four months before admission to the hospital there developed a swelling of the neck that increased rapidly in size and became quite tender. She was soon afflicted with spells of coughing, increasing in frequency, accompanied by a sense of suffocation, and with some dyspnea so that sleep was possible only when propped up in bed. There was no dysphagia. There has been a loss of 30 pounds in weight during the past four months, and for over 2 months the temperature varied between 99° and 100.5° F. The pulse was 104, there was a slight tremor, the eyes were negative, the teeth and tonsils were apparently diseased. The thyroid presented a lump on the left side which did not move on deglutition; the mass was tender, and the area swollen and hard as wool. The leucocyte count was 14,200; the Wassermann test was negative. A tentative diagnosis of malignancy was made. Following temporary improvement under x-ray and other measures, the patient grew steadily worse and marked cyanosis of the face and limbs with dyspnea and crowing inspiration developed 12 days after admission. Operation, with removal of a portion of the mass followed by tracheotomy, resulted in the saving of the patient from death by asphyxia. Pathological examination of the specimen excluded the existence of tuberculosis, syphilis, and malignancy, the final diagnosis being chronic thyroiditis with extensive fibrous encapsulation; in other words, ligneous thyroiditis due to infectious foci. The patient recovered.—I. B.

Myxedema and mental changes (Myxoedeme et psychose). Claude (H.) & Bernard (S.), Encéphale (Par.), 1924, **14**, 1-2.

A woman, aged 53, had delusions of persecution with terrifying sensory hallucinations, particularly visual; she was very depressed. She had the physical signs of myxedema. Under treatment there was amelioration of the myxedematous state and disappearance of the episode of melancholia. Interruption of the treatment resulted in swelling of the features, lowering of the basal metabolism and recurrence of the mental symptoms.—C. E. N.

Arteriosclerosis in thyroid deficiency. Fishberg (A. M.), J. Am. M. Ass. (Chicago), 1924, **82**, 463-464.

The case of a patient is reported who presented two seemingly discrete symptom complexes, an anatomic equivalent for each being found at the necropsy. He showed a hypertensive syndrome with a diastolic blood pressure of 135, cardiac hypertrophy and cerebral hemorrhage; corresponding to this there was found at the necropsy generalized arteriosclerosis and beginning primary contraction of the kidneys. Also there was sudden onset of adiposity of a peculiar distribution with retardation of skeletal and more particularly genital development, as well as abnormal distribution of hair. These phenomena point unequivocally to an endocrine disturbance, and at

nercopsy there was found a very extensive atrophy of the thyroid gland, with no other evident anomalies of the endocrine organs. The author thinks it probable that the cardiorenal and endocrine disturbances are correlated.—R. G. H.

Roentgen-ray therapy in the treatment of exophthalmic goiter. Goodwin (G. M.) & Long (W. B.), Am. J. M. Sc. (Phila.), 1924, **167**, 38-54.

The cases selected for this study were of the toxic exophthalmic type. They presented general enlargement of both thyroid lobes and isthmus, the swelling being diffuse and smooth. No case of toxic adenoma is included in this group since there seems to be little doubt that surgery is the proper method of treatment in this type. The roentgen-ray technic employed consisted in the administration of approximately two-fifths of an erythema dose, filtered through aluminum, to alternate sides of the neck each week. A uniform distance of 35 cm. from the target to the skin was used. Filtration was accomplished by 3 mm. of aluminum. The potential at the tube terminals was 140,000 volts, peak, corresponding to a spark gap of 10 inches between points. Five milliamperes were used, and the time of exposure uniformly 5 minutes, with the exception that in highly toxic cases this dose was still further reduced. The report includes 9 cases. In 5 the results of treatment have been satisfactory. In 1 the influence of treatment is doubtful, and in another no conclusion can be drawn because treatment was interrupted. In the 2 remaining cases the toxemia seemed to increase in spite of prolonged treatment. In the 5 favorable cases the authors are unable to speak of the permanency of benefit or tendency to recurrence of symptoms.—Am. J. Surg., **38**, 40.

Exopthalmic goitre in childhood with some unusual manifestations. Heiman (H.), Am. J. Dis. Child. (Chicago), 1923, **26**, 216-223.

Heiman gives a review of the literature and adds 3 cases of his own. He concludes that in the light of recent evidence the most rational procedure is to institute first a regimen of strict physical and psychical rest for 6 to 10 weeks. If the patient shows no improvement a short period of roentgen-ray therapy should be tried. Thyroidectomy should be performed if there is no response to roentgen rays. On account of the toxic action on the heart in severe cases it is safer not to wait too long before operation.—M. B. G.

A shadowgraph method of recording outlines of hands. Hoeffel (G. N.), Am. J. Dis. Child. (Chicago), 1923, **26**, 280-284.

The hand is firmly placed over a sheet of sensitized printing paper (Eastman's velox). A 110 volt, 100 watt Edison Mazda incandescent lamp is then placed 48 inches directly above the middle axis of the hand and the sensitized paper is exposed for 10 seconds.

This procedure should be carried out in a dimly lighted room. The print is then developed with the usual developing and fixing reagents. The relative proportion of the hand of the **cretin** and of the **mongolian idiot** show characteristic differences. Although the length of the hands is approximately the same, the length of the palm of the cretin is less than that of the mongolian, while the length of the fingers of the former is decidedly greater than that of the latter.—M. B. G.

Tuberculosis of the thyroid. Ito (H.), Chugwai Iji-Shimpo, 1923, No. 1027 (Jan.); Jap. Med. World (Tokyo), 1923, **3**, 106.

The author has seen only two other cases of this type reported in the literature, one by Schiller and the other by Pollag. Ito's subject was a 19 year old man. Diagnosis was established by histological examination of the extirpated thyroid. A fistula from the gland developed and through it pus escaped into the subcutaneous tissue, thus forming a cold swelling.—R. G. H.

Myxedema of the larynx. Josephson (E. M.), J. Am. M. Ass. (Chicago), 1924, **82**, 108-109.

Josephson reports the case of a woman, aged 42, whose chief complaint was orthopnea and a choking sensation in the throat, especially marked when lying flat on the back. The illness dated back to 1913; since then the patient had had a thick voice and had been afflicted with intermittent hoarseness, unaccompanied by cough, which is especially marked in wet weather. Laryngoscopic examination was rendered difficult by an extremely enlarged tongue that filled both mouth and pharynx. Below a large, well developed epiglottis was a mass of tissue springing, apparently, from the posterior wall of the larynx and the interarytenoid space, shutting off the view of the lower structures. This mass was deep red, and seemed to be ulcerated. Thyroid therapy was resolved on; progressively increased doses were given, beginning with one-half grain (0.0324 gm.) of the dried gland once a day, up to 2 grains (0.13 gm.) of the extract three times a day. Within two weeks the symptoms complained of disappeared completely. Laryngoscopic examinations now showed a very large larynx, supermasculine in its proportions, set deep in the throat. Under continued thyroid therapy the tissue of walls and prolapsed ventricle dwindled, leaving a spacious glottis and supraglottic regions. An interesting phase of the treatment was the steady improvement in volume of the voice, parallel to the diminution in size of the tongue, and in its pitch and timbre paralleled to the laryngeal improvement.—Courtesy A. M. A.

Preliminary report of the Kottmann reaction in children, with a note on the treatment of chorea with thyroid. Lyttle (J. D.) & Sutton (L. P.), Am. J. Dis. Child. (Chicago), 1923, **26**, 179-185.

This study is based upon the observations in 106 cases. In the control group of 28 cases, 21 gave normal reactions. The 3 retarded reactions could be explained upon the basis of medication with sodium bromid and calcium chlorid. Kottmann, Petersen and Merke also found that bromids prolong the reaction. In the group of acute infection 13 were normal, 15 accelerated and 5 retarded. In the group of cardiac children the predominating reaction was acceleration, probably from the lowered vitality of the children. In fifteen choreas the severe and moderate cases consistently showed accelerated reactions. Thyroid was administered with beneficial results in 9 cases. The endocrine and idiocy cases were too few in number to justify any definite conclusion as to the value of the Kottmann reaction; of the 19 in this group, 10 gave normal reactions. In detail, the results obtained were: **hypopituitary,** 5 normal and 1 accelerated; **thymus** and microcephalus, 1 normal; **cretin,** 2 accelerated; **hyperthyroid,** 1 accelerated and 1 retarded; **goiter,** 1 retarded; **dyspituitary,** 1 retarded; **idiots,** 4 normal, 2 accelerated. Petersen and others in a series of 400 cases obtained markedly retarded reactions in 65 out of 70 cases of hyperthyroidism and in 11 cases under bromid treatment, confirming Kottmann's findings. Petersen considers the reaction a close index of thyroid function and a reflection of the increased metabolism which occurs with hyperthyroidism. An accelerated reaction would therefore be expected with decreased basal metabolism. Kay felt that the reaction failed in cases of hypothyroidism, but that it gave definite indications of hyperthyroid conditions.—M. B. G.

Hyperthyroidism associated with acidosis. Major (R. H.), Med. Clin. N. Am. (Phila.), 1924, **7,** 1065-1068.

This is the report of the case of a colored female 49 years old whose chief complaints were nervousness, weakness, and loss of weight. Focal infections in tonsils and teeth were present. Three years before, following a severe fright, she became almost paralyzed with exhaustion, and within a few days a "lump in her neck" was observed. When the patient came to the writer's attention she presented a typical picture of **exophthalmic goiter,** with a basal metabolic rate 53% above normal. Two weeks after admission to the hospital she became irrational and quite toxic; the temperature was 100 F. and the pulse 160 per minute; the blood showed a carbon dioxide tension of 20 volumes percent, and the urine presented acetone and diacetic acid. Under the influence of sodium bicarbonate therapy and a 5% solution of glucose by rectum the patient's condition improved very rapidly. Within 8 hours she became very much less toxic and within 24 hours the evidences of acidosis had disappeared. The author believes that acidosis complicating hyperthyroidism is frequently overlooked.—I. B.

Goiter in the Great Basin. Middleton (G. W.), Calif. State J. M. (San Fran.), 1924, **22**, 52-54.

In the Virgin Basin of southern Utah 75% of the women have some form of thyroid enlargement, and in many instances large goiters remain untreated throughout life. In the Salt Lake Valley, on the other hand, due to proximity to saline waters, goiter is a relatively uncommon condition. Treatment depends upon the nature of the thyroid growth. Of the 213 subjects seen and treated by the author, 111 were operated upon; the remainder, largely of the colloid type, were treated nonsurgically.—I. B.

Methods of administering iodine for prophylaxis of endemic goiter. Olesen (R.), Pub. Health. Rep. (Wash.), 1924, **39**, 45-55.

Summarizing available evidence Olesen concludes that while numerous methods of supplying iodine for the prevention of endemic goiter have been suggested, the most favored one at the present time is the administration of a chocolate tablet containing 10 mgs. of iodine in the form of an organic acid. One or two of these tablets, according to the age and requirements, should be given each week during the school year to both boys and girls between the ages of 11 and 16. Owing to the presence of thyroid enlargements in children less than 11 years of age, prophylaxis should profitably begin earlier than has ordinarily been recommended. The preventive should be used both in children in whom there is no evidence of thyroid enlargement and in those having such enlargement. In the latter instance, however, the exercise of nominal medical supervision is desirable. The iodine-chocolate combination or other iodine-containing mixtures may be used advantageously during pregnancy, under the direction of a physician. While individual oral administration of iodine is the method generally employed, the use of iodized table salt holds forth considerable promise as an efficient means of preventing endemic goiter in a wholesale manner. However, the difficulties of gauging accurately the dosage and of excluding from treatment the hypersusceptible are manifest handicaps to its uncontrolled application. The wholesale iodization of a municipal water supply may be cited as an ingenious method in need of further appraisal before a definite verdict as to its efficiency can be given. According to the best information available there is little, if any, danger in iodine prophylaxis when it is carried out intelligently. Moreover, the rationale of the procedure is sufficiently sound and the results are sufficiently marked to make its extensive application both justifiable and advisable.—Author's summary.

Th end results of surgery of the thyroid gland. Pemberton (J. deJ.), Arch. Surg., 1923, **7**, 37-46.

In 1922 in the Mayo Clinic 1,983 operations were performed on 1,497 patients with goiter with mortality from operation of 0.95%

and by case of 1.2%. Classification of operable thyroid condition is as follows: (1) Diffuse colloid goiter—the common physiological thyroid enlargement in adolescence, producing no symptoms beyond those of pressure, iodine deficiency being the etiological factor. (2) Adenoma without hyperthyroidism. In a small proportion of cases enlargements are entirely concealed in the thoracic cavity. Operative procedure is the only effective remedy. (3) Adenoma with hyperthyroidism. This is not to be confused with exophthalmic goiter. The symptoms of hyperthyroidism usually occur spontaneously and develop gradually but progressively. These symptoms may be induced abruptly by the administration of iodine to a patient with adenoma without hyperthyroidism. The operative mortality is between 2 and 4%. Judd found after 2 years 83% considered themselves cured and 5% more were markedly improved. (4) Exophthalmic goiter. This is characterized by an increased basal metabolic rate, by a peculiar nervous syndrome and usually by exophthalmos, with a tendency to gastric intestinal crises of vomiting and diarrhea. The cause of exophthalmic goiter is unknown, but there is always the characteristic pathologic picture of diffuse parenchymatous hypertrophy and hyperplasia in the thyroid gland. Operation has particular danger just before, during, and following a crisis. In 1922 there were 1,093 operations on 633 patients with exophthalmic goiter in the Mayo Clinic; 11 died; there was operative mortality of 1.005%; by case, 1.74%. Wilson found in the Mayo Clinic 1 case of malignancy in 57. Recent rapid growth in the thyroid suggests malignancy. Wide surgical removal followed by radium or roentgen ray offers the best chance. In a study of 207 cases of malignancy up to January, 1921, the Mayo Clinic gave:

Sarcoma	19 cases no cures
Carcinoma	62 cases 5%, 5 year cures
Malignant adenoma	102 cases 20%, 5 year cures
Malignant papilloma	24 cases 33%, 5 year cures

—Am. J. Roentgol., **11**, 112.

Roentgen-ray therapy in thyrotoxicosis; its effect as measured by the basal metabolic rate. Read (J. M.), Calif. State J. M. (San Fran.), 1924, **22**, 10-15.

A report of the results of x-ray therapy on all forms of goiter associated with an increased metabolic rate, based upon a series of 50 cases. Although in toxic adenoma operation is a logical procedure, this is far from the case in the treatment of the **Graves' syndrome.** It is therefore extremely important clearly to differentiate the two conditions prior to the institution of treatment. The roengen ray seems to be effective in at least improving thyrotoxicosis as proved by the reduction in the basal metabolic rate. This is usually accomplished in from 3 to 6 months of treatment.—I. B.

A relationship of blood sugar to thyroid and suprarenal size in a fraternity of pigeons. Riddle (O.), Honeywell (H. E.) & Spannuth (J. R.), Am. J. Physiol. (Balt.), 1924, **67**, 539-546.

In a group of brother and sister hybrid pigeons, those with abnormally low blood sugar had large thyroids and large suprarenals. Abnormally high sugar was associated with small thyroids and suprarenals. Less conclusive evidence points to large gonads associated with large thyroids.—T. C. B.

X-ray treatment of lesions of the thyroid gland. Williams (J. G.), Long Island M. J. (Brooklyn), 1923, **17**, 353-359.

Toxic adenoma responds readily to the roentgen ray, but surgery is quicker and the mortality in these cases is low. The technique has been to treat the thyroid and thymus areas on each side separately with 4 mm. of aluminum as a filter, a 9-inch spark-gap, at a distance of 9 inches, for 6 minutes to each area. Latterly, where the tonsils showed marked hypertrophy, Williams has included them in the area to be treated, extending the distance to 12 inches and time to 9½ minutes. The second treatment is given 3 weeks later, and a third treatment 4 weeks after the second, the interval between treatments being extended one week longer than each preceding interval. Usually, at the third visit, 7 weeks after the first treatment, there is noted a slowing of the pulse rate and an amelioration of the nervous symptoms. After this, the patient begins to regain some of the previous loss in weight. The eye symptoms and the goiter are the last to show improvement, and frequently do not wholly disappear. The author says that patients treated surgically do better and the risk of operation is less if they had previously had their thymus glands irradiated.—Am. J. Roentgenol., **11**, 103.